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PATENT
1817-113P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Igor SHVETS et al.	Conf.:	4598
Appl. No.:	09/927,355	Group:	1762
Filed:	August 13, 2001	Examiner:	NOT ASSIGNED
For:	A METHOD AND DEVICE FOR DISPENSING OF DROPLETS		

LETTER

Assistant Commissioner for Patents
Washington, DC 20231

April 15, 2002

Sir:

Under the provisions of 35 U.S.C. § 119 and 37 C.F.R. § 1.55(a), the applicant(s) hereby claim(s) the right of priority based on the following application(s):

Country	Application No.	Filed
IRELAND	2001/0457	May 11, 2001

A certified copy of the above-noted application(s) is(are) attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Paul C. Lewis

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JMS:MTS/mks
1817-113P

Attachment

Patents Office
Government Buildings
Hebron Road
Kilkenny

I HEREBY CERTIFY that annexed hereto is a true copy of documents filed in connection with the following patent application:

Application No.	2001/0457
Date of Filing	11 May 2001
Applicant	ALLEGRO TECHNOLOGIES LIMITED, an Irish Company of Innovation Centre, O'Reilly Institute, Trinity College, Dublin 2, Ireland.

Dated this 22 day of June 2001.

CO'Reilly

PP An officer authorised by the
Controller of Patents, Designs and Trademarks.

FORM NO. 1

REQUEST FOR THE GRANT OF A PATENT

PATENTS ACT 1992

0 1 0 4 5 7

The Applicant(s) named herein herby request(s)
[X] the grant of a patent under Part II of the Act
[ ] the grant of a short-term patent under Part III of the Act
on the basis of the information furnished hereunder.

1. Applicant(s)

ALLEGRO TECHNOLOGIES LIMITED
Innovation Centre
O'Reilly Institute
Trinity College
Dublin 2
Ireland
an Irish Company

2. Title of Invention
A Method and Device for dispensing of droplets

3. Declaration of Priority on basis of previously filed application(s) for same invention (Sections 25 & 26)

Previous Filing Date	Country in or for which filed	Filing No.

4. Identification of Inventor(s)

Name(s) and addresse(s) of person(s) believed by the Applicant(s) to be the inventor(s)

01045?

5. Statement of right to be granted a patent (Section 17(2) (b))

To Follow

6. Items accompanying this Request

(i) [X] prescribed filing fee (IRP 100)
(ii) [X] specification containing a description and claims
[ ] specification containing a description only
[X] Drawings referred to in description or claims
(iii) [ ] An abstract
(iv) [ ] Copy of previous application(s) whose priority is claimed
(v) [ ] Translation of previous application whose priority is claimed
(vi) [X] Authorisation of Agent (this may be given at 8 below if this Request is signed by the Applicant(s))

7. Divisional Application(s)
The following information is applicable to the present application which is made under Section 24 -

Earlier Application No.
Filing Date:

8. Agent

The following is authorised to act as agent in all proceedings connected with the obtaining of a patent to which this request relates and in relation to any patent granted -

Name & Address

Cruickshank & Co. at their address recorded for the time being in the register of Patent Agents is hereby appointed Agents and address for service, presently 1 Holles Street, Dublin 2.

9. Address for service (if different from that at 8)

Signed Cruickshank & Co.

By:- Executive.

Agents for the Applicant

Date 11/ 5/2001

APPLICATION No. 010457

A Method and Device for Dispensing of Droplets

Introduction

The present invention could be used in fields such as drug development, pharmaceutical, medical diagnostics, biotechnology, analytical chemistry and others. It is generally related to liquid handling systems and in particular to systems for dispensing and aspirating small volumes of liquids. It is particularly directed to High Throughput Screening (HTS), Polymerase Chain Reaction (PCR), combinatorial chemistry, microarraying, proteomics and other similar tasks. In the area of high throughput screening, PCR, proteomics and combinatorial chemistry, the typical application for such a liquid handling system is in dispensing of small volumes of liquids, e.g. 5 microlitres and smaller and in particular volumes around 1 microlitre and smaller. The invention is also directed to aspiration of liquids from sample wells so that the liquids can be transferred between the wells. The invention relates also to microarray technology, a recent advance in the field of high throughput screening and genomics. Microarray technology is being used for applications such as DNA and protein arrays: in this technology the arrays are created on glass or polymer slides. The invention can also be used for simultaneous aspiration and dispensing of a multiplicity of liquids. Such a simultaneous aspiration and dispensing can be required for rapid filling of well plates or plates containing blocks of analytical devices for parallel processing of a range of liquids. The well plates filled with a range of liquids can in turn be coupled to a variety of analytical devices such as electrophoresis analyzers, chromatographers, mass spectrometers and others. Many of these areas of application require routine dispensing of consistent droplets of liquids of submicrolitre volume, in some cases down to only a few nanolitres in volume. The present invention is also directed to medical diagnostics e.g. for applications such as single nucleotide polymorphism or others.

Development of instrumentation for dispensing of minute volumes of liquids has been an important area of technological progress for some time. Numerous

devices for controlled dispensing of small volumes of liquids (in the range of 1μl and smaller) for ink jet printing application have been developed over the past twenty-five years. More recently, a wide range of new areas of applications has emerged for devices handling liquids in the low microlitre range.

The requirements applied to a dispensing system vary significantly depending on the application. For example, the main requirement of a dispensing system for ink jet applications is to deliver droplets of a fixed volume with a high repetition rate. The separation between individual nozzles should be as small as possible so that many nozzles can be accommodated on a single printing cartridge. On the other hand, in this application the task is simplified by the fact that the mechanical properties of the liquid dispensed namely ink are well-defined and consistent. Also in most cases the device used in the ink jet applications does not need to aspire the liquid through the nozzle for the dispenser refill.

For biomedical applications such as High Throughput Screening (HTS), the requirements imposed on a dispensing system are different. The system should be capable of handling a variety of liquids with different mechanical properties e.g. viscosity. Usually these systems should also be capable of aspiring liquids through the nozzle from a well or other source. On the other hand there is not such a demanding requirement for the high repetition rate of drops as in ink jet applications. Another requirement in the HTS applications is that cross contamination, between different wells served by the same dispensing device, be avoided as much as possible.

The most common method of liquid handling for the HTS applications is based on a positive displacement pump such as described in US Patent Specification No. US 5,744,099 (Chase et al). The pump consists of a syringe with a plunger driven by a motor, usually a stepper or servo-motor. The syringe is usually connected to a nozzle of the liquid handling system by means of a flexible polymer tubing. The nozzle is typically attached to an arm of a robotic system that carries it between different wells for aspiring and dispensing the liquids. The syringe is filled with a system liquid such as water. The system liquid continuously extends through the

flexible tubing down towards the dispenser. The sample liquid that needs to be dispensed, fills up into the dispenser from the tip. In order to avoid mixing of the system liquid and the sample liquid and therefore cross-contamination, an air bubble or bubble of another gas is usually left between them. In order to dispense the sample liquid from the nozzle, the plunger of the syringe is displaced. Suppose this displacement expels the volume ΔV of the system liquid from the syringe. The front end of the system liquid filling the nozzle is displaced along with it. The system liquid is virtually incompressible. If the inner volume within the flexible tubing remains unchanged, then the volume ΔV displaced from the syringe equals the volume displaced by the moving front of the system liquid in the nozzle. If the volume of the air bubble is small it is possible to ignore the variations of the bubble's volume as the plunger of the syringe moves. Thus, the rear end of the sample liquid is displaced by the same volume ΔV in the nozzle, and therefore the volume ejected from the tip is the same ΔV. This is the principle of operation of such a pump. The pump works sufficiently accurately if the volume ΔV is much greater than the volume of the air bubble.

In practice, the volume of the air bubble changes as the plunger of the syringe moves. Indeed in order to eject a drop from the tip, the pressure in the tubing should exceed the atmospheric pressure by an amount determined by the surface tension acting on the drop before it detaches from the nozzle. This is discussed in more detail below. Therefore, at the moment of ejection the pressure in the tubing increases and after the ejection, it decreases. As common gasses are compressible, the volume of the air or gas bubble changes during the ejection of the droplet and this adds to the error of the accuracy of the system. The smaller the volume of the air bubble, the smaller is the expected error. In other words the accuracy is determined significantly by the ratio of the volumes of the air bubble and the sample liquid droplet to be dispensed. The smaller this ratio is the better the accuracy. For practical reasons it is difficult to reduce the volume of the air or gas bubble to below some one or two microlitres and usually it is considerably greater than this. Therefore, this method with two liquids separated by an air or gas bubble and based on a positive displacement pump is not well suited for dispensing a small volume of the order of 1 microlitre or lower.

There are also additional limitations on accuracy when sub-microlitre and low microlitre volumes need to be dispensed. For example, there is an issue of disconnection of the drop from the tip. The drop is attached to the tip and held there by surface tension. In order to overcome this problem the plunger of the syringe is displaced, usually at a high speed. The front end of the sample liquid is displaced along with it. At some moment the syringe pump is stopped nearly instantaneously, and the rapid deceleration of sample liquid at the tip separates the droplet from the tip. Even when this method of drop detachment works well, fast movement of the plunger adds to the pressure variation in the gas bubble separating the two liquids through the inertia of the sample liquid in the tip moving with acceleration and deceleration. In practice, this method does not work reliably for drops with volume smaller than approximately one microlitre. To dispense such small drops, the tip is often brought into mechanical contact with the substrate increasing the chance of cross-contamination. For larger droplets, fast movement of the plunger of the syringe pump as required for the disconnection of the drop from the tip, can cause splattering of the liquid ejected. For many applications this is highly undesirable.

Conventional dispensers based on syringe pumps are susceptible to cross-contamination. As explained above, there is an air bubble separating the sample liquid from the system liquid. As the volume of the air bubble is reduced, the chances of cross-contamination increase. Indeed, during the dispensation step, the system liquid can arrive into the part of the dispenser from which the sample liquid has been just expelled. As a result the system liquid can become contaminated with traces of sample liquid. Then, during the aspiration step, the sample liquid can arrive into the part of the dispenser from which the system liquid has been just expelled. As a result, a cross-contamination can occur even if the air bubble separates the two liquids at any given moment.

Other examples of such positive displacement pumps are shown in US Patent Specification No. 5744099 (Chase et al). Similarly the problems of dispensing drops of small volume are also described in U.S. Patent Specification Nos. 4574850 (Davis) and 5035150 (Tompkins). The particular aspect of the problem

addressed in No 5035150 is sticking of droplet to the tip. The solution proposed in this patent is to enhance pressure variation in the tubing joining the pump with the dispenser during the drop dispensing. This is achieved by using an electromagnetic valve installed in the line. As the plunger of the positive displacement pump moves forward to expel the sample liquid from the tip, the valve is closed. The pressure builds up in the tubing compressing the air bubble. Then the valve is open allowing the air bubble to expand. The air rushes out of the tip creating an air stream causing the drop off of the sample liquid.

U.S. Patent Specification No. 5741554 (Tisone) describes another method of dispensing submicrolitre volumes of liquids for biomedical application and in particular for depositing bodily fluids and reagents on diagnostic test strips. This method combines a positive displacement pump and a conventional solenoid valve. The positive displacement pump is a syringe pump filled with a liquid to be dispensed. The pump is connected to a tubing. At the other end of the tubing there is a solenoid valve located close to the ejection nozzle. The tubing is also filled with the liquid to be dispensed. In this method the piston of the pump is driven by a motor with a well-defined constant speed. The speed determines the flow rate of the liquid from the nozzle provided the solenoid valve is opened frequently enough and the duty cycle between opening and closing of the valve is long enough. The solenoid valve is actuated with a defined repetition rate. The repetition rate of the valve and the flow rate of the pump determine the size of each drop. For example, if the pump operates at a flow rate of 1μl per second and the repetition rate is 100 open-close cycles per second, then the size of each drop is 10 nl. This method is suitable for dispensing of large number of identical droplets. However, for dispensing of liquids for HTS applications, this method is often inappropriate since it is commonly required to aspire a liquid through the nozzle in small quantities (say 1 μl) and then dispense it in fractions of this quantity, say in a series of only five drops or even a single drop on demand. To avoid mixing of the liquid aspired with the one in the syringe pump, it is probably necessary to place a bubble of gas in the tube with the attendant problems described above.

Without such a bubble, if the solenoid valve open time and/or operating frequency

are too small for a given pump flow rate, the pressure in the dispenser will become too great, causing possible rupture or malfunctioning of the system. Another disadvantage of this solution is that the heat from the coil actuating the plunger of the valve may cause the heating effect of the liquid in the valve that can be a serious problem for some applications. Besides, for some regimes of operation the drops may amalgamate, e.g. one drop will be released for every two or three actuations of the valve.

This patent [US No 5,741,554; 1998] also describes the combinations of positive displacement pump with a piezo electric dispenser and air-brush dispenser.
Drops of microlitre volume and smaller can be also generated by the method of electrospray which is mainly used for injection of a liquid into a chemical analysis system such as a mass spectrometer. In most cases the desired output of an electrospray system is not a stream of small drops but rather of ionised molecules. The method is based on supplying a liquid under pressure through a capillary tube towards its end or tip and then a strong electrostatic field is generated at the tip by applying a high voltage, typically over 400V, between the tip of the capillary and a conductor placed close to it. A charged volume of liquid at the tip of the capillary is repelled from the rest of the capillary by Coulomb interaction as they are both charged with the like charge. This forms a flow of charged particles and ions in the shape of a cone with the apex at the tip of the capillary. A typical electrospray application is described in US Patent Specification No. 5115131 (Jorgenson et al). There are inventions where the droplets emitted from a capillary are charged in order to prevent them from coming together with coagulation. This approach is described in US Pat No 5,891,212 (Tang et al) for the fabrication of uniform charged spheres. US Pat. No 4,302,166 (Fulwyler et al) teaches how to handle uniform particles each containing a core of one liquid and a solidified sheath. In this latter invention, the electric field is applied in a similar way to keep the particles away from each other until the sheath of the particles has solidified. In this invention the particles are formed from a jet by applying a periodic disturbance to the jet. US Pat. No 4,956,128 (Martin Hommel et al) teaches how to dispense uniform droplets and convert these into microcapsules. A syringe pump supplies the fluid into a capillary. A series of high voltage pulses is applied to the capillary.

The size of the droplets is determined by the supply of fluid through the capillary and the repetition rate of the high voltage pulses. The specification does not discuss generation of a single drop on demand. In the patent specification No 4,956,128 there is no distinction between the sample liquid and the system liquid. The sample liquid fills up all the volume in the capillary (dispenser), the syringe and the tubing joining the two. US Pat. No 5,639,467 (Dorian et al) teaches a method of coating of substrates with a uniform layer of biological material. A droplet generator is employed which consists of a pressurised container connected to a capillary. A high constant voltage is applied between the capillary and a receiving gelling solution.

There is one additional relatively recent requirement to a liquid handling system that now becomes increasingly important. It is vital for many applications, that the liquid handling system can dispense liquids containing suspensions of hard particles called beads. Typical beads have the size of some 10 to 100 micron although beads with sizes outside this range can also be used. Some of them are ceramics-based and others are made of ferromagnetic materials, e.g. magnetic particles King FisherTM from Labsystems Oy, P.O. Box 8, FIN-00881, Helsinki, Finland. Dispensing liquids with beads in the low microlitre volume is a highly challenging task. In addition to all the complications described in detail above, dispensing beads using a solenoid valve can block the valve seat of the valve. Dispensing the beads using dispensers based on piezoelectric actuators as used in ink jet printing, is also complicated. In this case the beads present inhomogeneities with volume comparable with the volume of a drop produced by many such dispensers. Dispensing magnetic beads presents additional difficulties for the solenoid valve-based dispensers. The reason is that the magnetic beads can aggregate in areas of strong gradient of magnetic field inside the valve. Thus the drops of liquid dispensed are depleted of magnetic beads. The valve itself can malfunction as it accumulates a significant quantity of magnetic material inside.

In summary of the above analysis, the most common method of handling reagents used in HTS and similar applications is based on a positive displacement pump and a gas bubble. The problem is that when dispensing volumes of reagents around 1

microlitre or smaller the variation in the volume of the bubble during the dispensation compromises the accuracy. The drop attachment to the tip of the dispenser by surface tension also causes a problem when dispensing submicrolitre drops. It has been found difficult to eject small droplets of precisely required volume using this method.

As the size of wells becomes smaller and smaller, the problem of missing the correct well or dropping the liquid reagent at a wrong location of the target substrate becomes more and more significant. In order to improve the accuracy of "shooting" with drops, the tip of the dispenser should be brought closer to the bottom of the well. However, as the distance between the tip and the bottom of the well decreases, the chances of cross contamination increase.

Measurement of the volume of the drops dispensed in the submicrolitre range is a formidable task. It would be a highly desirable and valuable feature of a liquid handling instrument to be capable of measurement of volume of individual droplets especially in the submicrolitre range, and also measurement of the dispensation event that would allow to confirm that the drop has been dispensed.

US Patent No. 5,559,339 (Domanik) teaches a method for verifying a dispensing of a liquid from a dispenser. The method is based on coupling of electromagnetic radiation that is usually light from a source, to a receiver. As a droplet of liquid travels from the dispenser it obstructs the coupling and therefore the intensity of the signal detected by the receiver is reduced. The mechanism of such an obstruction is absorption of electromagnetic radiation by the droplet. The disadvantage of this method is that the smaller the size of the droplet, the smaller is the absorption in it. Almost certainly the method will not work for fluids that do not absorb the radiation. For a range of applications such as high throughput screening where minute droplets of liquids with a broad range of optical properties need to be dispensed, the methods disclosed in this specification are inappropriate. Further the specification acknowledges that it will only operate satisfactorily with major droplets.

In summary, there is a major problem in finding a suitable way of dispensing submicrolitre volumes for applications as described above such as HTS applications. This problem can be said to be currently the bottleneck in changing to assay formats of higher density. Numerous publications in the specialized literature indicate that a technical solution to this problem has not been found so far. For example, according to surveys carried out by the journal Genetic Engineering News (Vol. 20, No. 2, Jan 2000), absence of an adequate technology for low volume liquid dispensing is named as the number one reason preventing researchers from moving to denser microplates.

The present invention is directed towards providing an improved method and apparatus for dispensing of volumes of liquids as small as 10 nl = 10^{-8}l or even smaller, while at the same time it should be possible to dispense larger droplets such as those as large at 10 microlitres or even greater.

Another objective is to provide a method where the quantity of the fluid dispensed can be freely selected by the operator and accurately controlled by the dispensing system. The system should be capable of dispensing a drop of one size followed by a drop of a widely differing size, for example, a 10 nl drop followed by a 500 nl one. This is in contrast to for example ink jet printing where the volume of one dispensation is fixed, and dispensations are only possible in multiples of this quantity.

Another objective is to provide a method where cross contamination between different liquids handled by the same dispenser is reduced.

Yet another objective of the invention is to provide a liquid handling device and method in which the dispenser does not carry an uncontrolled droplet of liquid attached to its tip during the aspiration. Therefore, this will allow reducing wastage of valuable liquids and improving accuracy of the very first dispensation after the aspiration.

Another objective is to reduce the priming volume of the dispenser. The priming volume is understood to be the volume of liquid that must be placed inside the dispenser, e.g. aspirated by the dispenser before it can function properly and deliver the dispensations accurately.

Yet, another objective is to reduce the “dead” volume of the dispenser, that is the volume that cannot be returned back into the target substrate after the complete aspirate-dispense cycle. It should be notices that the notions of “dead” volume and priming volume are related although the specific relation depends on the relevant definitions of these terms. The relevant definitions of the terms of “dead” volume and priming volume may to a certain extent depend on the protocol of the aspirate/dispense cycle.

The invention is also directed towards providing a method where the liquid can be dispensed on demand, i.e. one quantity can be dispensed at a required time as opposed to a series of dispensations with set periodic time intervals between them. Yet, the method should also allow for dispensation of doses with regular intervals between subsequent dispensations, for example, printing with reagents.

Another objective of the present invention is to provide a method and a device suitable for dispensing a liquid from a supply line to a sample well and also for aspiring a liquid from the sample well into the supply line. The device should be able to control accurately the amount of the liquid aspired into the nozzle of the dispenser from a supply well.

Another objective is to provide a low cost front end of the dispensing device called herein the dispenser that could be disposed of when it becomes contaminated namely the part that comes in direct contact with the reagents dispensed.

Another objective is to provide a method for handling liquids in a robotic system for high throughput screening, proteomics or microarraying that would be suitable for

accurate dispensing and aspiring volumes smaller than the ones obtainable with other mainstream technologies.

Yet another objective is to provide means of more accurate delivery of a drop of liquid reagent to a correct target well on a substrate and also to improve the accuracy of delivery of the drop to a correct location in a well forming part of a receiving substrate.

Yet another objective is to provide means for directing doses of liquids into different wells of a sample well plate and means of controlling the delivery address of the dose on the sample well plate to speed up the liquid handling procedure.

Another objective is to provide means for dispensing of small drops of suspensions of particles including magnetic particles such as magnetic beads.

Yet another objective of the invention is to reduce “splashing” as the drop arrives at the well.

Another objective of the invention is to provide information if the drop was dispensed or not, validation of the drop dispensation. It is additionally an objective to measure the volume of the drop dispensed.

Yet another objective is to provide means for simultaneous aspiration and simultaneous dispensation of a range of different sample liquids without cross-contamination thus enabling a multi-channel dispenser.

Statements of Invention

The invention is based on the fact that accurate syringe pumps are capable of metering volumes of liquids well below one microlitre. The smallest volume that can be metered by a syringe pump depends on the overall volume of the syringe and precision of the mechanical system driving the plunger of the syringe. A syringe

pump having even a relatively low accuracy of the mechanical system, is usually capable of ejecting volume of the syringe in at least 1000 steps or more. Therefore, if e.g. a small syringe with the volume of some 10 micrlolitre is used with the pump, then the smallest volume that can be metered by the pump is 10 nl. The volume of 10 nl is some 100 times smaller than the dispensing limit of current liquid handling systems using syringe pumps. The reason why the accuracy of the syringe pumps is not fully used at present, is explained in the description of the state-of-the-art in this specification.

Our invention uses the potential accuracy of a syringe pump to the full extent. The invention is based on the commonly overlooked fact that many elastomers although being soft and having low Young's modulus, are still virtually incompressible. For example, during a uniaxial strain deformation, as the length of the elastomer increases, its width and breadth decrease keeping its volume almost unchanged. The ratio of the fractional width change to the fractional length change is given by the Poisson ratio. For many elastomers, it is almost equal to 0.5. Those familiar with mechanics of deformations will appreciate that for materials with the Poisson ratio equal to 0.5, the volume change of the material during such deformations is very small. During a deformation caused by an isotropic pressure applied to the material, its volume change is given by the so-called bulk modulus. Bulk modulus is defined as $\Delta P/(\Delta V/V)$ where ΔV is the volume change of a piece of material having volume V in response to the pressure change ΔP applied to it. High value of the bulk modulus means that the material is almost incompressible during isotropic deformation caused by homogeneous pressure. Once again, many elastomers, have very high values of bulk modules. For example, for many materials the bulk modulus is of even greater than the value for water (0.21×10^{10} N/m^2).

The concept of the dispenser is as follows. There are two reservoirs: the system liquid reservoir and the sample liquid reservoir. They are separated by means of a flexible membrane or an expandable bag. The syringe pump communicates with the system liquid reservoir. The sample volume reservoir communicates with a nozzle. The system liquid reservoir is preferably entirely filled with a liquid such as water. As most liquids are practically uncompressible, the volume of the system

liquid reservoir remains constant irrespective of the position of the plunger of the syringe pump. As explained above, the volume of the material of the membrane or the expandable bag positioned between the system and sample reservoirs is also practically constant. Therefore, by moving the plunger, we can expel a well-defined volume of sample liquid from the nozzle that is exactly equal to the volume displaced by the syringe pump. This sample liquid could be separated from the nozzle to form a drop if the expelled volume is large enough or alternatively it will be suspended at the tip of the nozzle. We then detach the droplet by electrostatic drop off, by sending the pulse of mechanical disturbance to the nozzle or by directly contacting the substrate by the nozzle.

The invention could be split into four constituent parts:

1. Means for control of the volume of the sample liquid expelled from the nozzle.

2. Means for the drop detachment from the nozzle

3. Means for electrostatic droplet navigation.

4. Means for measurement of the volume of the drop dispensed and confirmation of the dispensation event.

Parts 3 and 4 can only be used if the drop detachment is based on electrostatic pull off.

These four parts effectively correspond to the four different stages in the drop dispensing process. They are described more in detail below.

Means for controlling the volume of the droplet is based on a syringe pump. The pump is usually driven by a motor/actuator. The syringe pump is hydraulically connected to a dispenser by means of nonexpandable tubing. A nozzle terminating in a tip is hydraulically connected at the other end of the dispenser. At least one flexible membrane or an expandable bag is installed in the dispenser to separate the syringe from the nozzle. The space between the syringe and the membrane/expandable bag is preferably entirely filled up with a system liquid such as water. The space on the other side of the membrane (or the expandable bag) forms the reservoir for the sample liquid. There are also optional elements such as pressure sensor, release valve, system liquid supply means all hydraulically connected to the syringe pump. It is highly advantageous that all the boundaries of the volume for the system liquid between the syringe pump and the dispenser consist of nonexpendable elements except for the membrane (or expandable bag). Therefore, the flexible membrane (or the expandable bag) is the only element that can accommodate the excess system liquid expelled from the syringe pump. As the volume of the membrane/expandable bag is unchanged, the volume of the sample liquid expelled from the tip is equal to the volume of the system liquid expelled from the syringe.

If the volume of the sample liquid expelled from the tip is small, e.g. 500 nl or smaller, the drop may not get detached from the tip. Instead it will be suspended at the tip by surface tension. Then the volume expelled can be transferred to the target substrate by bringing the suspended drop into a mechanical contact with the target substrate. This however may result in cross-contamination. To reduce the risk of cross-contamination, a number of non-contact methods are proposed in this invention. They are based on sending a compression wave to reach the tip of the nozzle and the droplet of the sample liquid suspended at the tip. If the compression wave has sufficiently large amplitude, it can detach the suspended drop from the tip. The compression wave can be generated by a piezo actuator or magnetic actuator that is mechanically coupled to the sample liquid reservoir, the system liquid, the nozzle or coupled to more than just one of these areas. Alternatively, a magnetostrictive actuator could be employed to excite a compression wave in the sample liquid. The principle of the magnetostricitve actuator is based on a change

in dimensions of a magnetostrictive element in the actuator in response to change in magnetic field applied to it. Therefore, by generating a pulse of magnetic field around the actuator, one can excite a mechanical compression wave in the sample liquid if the actuator is coupled mechanically into the dispenser.

In order to facilitate the detachment of the drops from the nozzle we can use electrostatic drop off. For this purpose we generate a pulse of a strong electrostatic field at the nozzle. This could be done e.g. by generating a pulse of high voltage from the voltage controller. The electrostatic field polarizes the drop at the nozzle and in this way an electrostatic repulsive force is created between the drop and the nozzle. This force causes the drop off. Therefore, the method of dispensing small drops using electrostatic drop off could be summarized as follows: we first grow the drop of required volume using a syringe pump. We then generate a pulse of a strong electrostatic field at the tip. As the value of the field increases during the pulse from the initial value to the final pre-set value, at some stage it will exceed the critical value causing the drop off. The critical value is mainly determined by the volume of the drop to be dispensed, diameter of the nozzle and surface tension.

Numerous arrangements could be devised for generating electrostatic field in the vicinity of the tip. The field is created between the tip of the dispenser and the drop off electrode or a plurality of drop off electrodes positioned in the vicinity of the tip. For practical reasons it can be advantageous that either liquid in the dispenser or the drop off electrode/electrodes are connected to the ground potential and the remaining of the two elements is connected to a high potential. Numerous arrangements of the drop off electrodes could be devised.

As the size of the wells receiving drops gets smaller and smaller, it is increasingly more difficult to ensure that the drop reaches the correct destination as it is ejected from a liquid handling system. For applications such as high-density arrays, the separation between the subsequent drops covering the substrate should be as small as 0.2 mm. In this invention there are means of controlling the destination of

the drop based on the electrostatic forces acting on the drop as it travels between the nozzle and the well. These means can be used in conjunction with electrostatic drop off.

In one case, for generating the electrostatic field as described above we use a drop off electrode positioned underneath the well. For accurate navigation, the size of the electrode is smaller than the size of the well. It may be advantageous to have the drop off electrode in the shape of a tip to produce the strongest electric field at the centre of a destination well. The electrode produces a strong electric field underneath the well attracting the drop to the required destination position (e.g. centre of the well). The drop off electrode may be attached to an arm of a positioner capable of moving it underneath the well plate and pointing to the correct destination well. Alternatively, the sample well plate may be repositioned above the drop off electrode in order to target a different well. It may well be necessary to move the tip and drop off electrode synchronously. It may be advantageous to have a module equipped with a number of drop off electrodes that could be connected to the high voltage supply independently. The distance between the electrodes could be e.g. identical to the distance between the centers of the wells in a well plate. In this case the drops could be navigated to different wells without actually moving the tip or the drop off electrode. This could be achieved by selectively charging the correct electrode to send the droplet in the required direction.

In another case the deflection electrodes are positioned along the path between the nozzle and the destination well. The electrodes are charged by means of a high voltage applied to them. As the drops leaving the tip are charged by the voltage between the tip and the drop off electrode, they will be deflected by the deflection electrodes.

It is important to realize that during the electrostatic drop off, the electrostatic force acting on the drop could be much greater than the gravity force. In this case as the drop travels between the nozzle and the substrate, the direction of the path is given

effectively by the direction of the electrostatic field, i.e. the field line initiated at the nozzle.

For independent measurement of the drop volume, one could use means described in EP application No 00650123.3. These include electromagnetic balance based on a coil suspended in a magnetic field or another suitable balance.

If electrostatic field is used for the drop off, one could also use all the methods of measurement of volume of the drop that are based on measuring its charge. These methods employ Faraday pail or bottomless Faraday pail. One could independently measure the electrostatic field required for the drop off and then work out from the field, volume of the drop using calibration dependencies. This could be achieved through independent monitoring of moment of the drop off while the electrostatic field in the vicinity of the nozzle is ramped up to cause the drop off. Monitoring of the moment of the drop off could be achieved by e.g. coupling electromagnetic radiation from a source to a detector through the drop suspended at the tip and monitoring the change in signal received by the detector caused by the drop off. One could also monitor the moment of drop off by using a Faraday pail. These methods are described in detail in EP application No 00650123.3 and US application No 09/709,541.

Detailed Description of the Invention

The invention will be more clearly understood from the following description of some embodiments thereof given by way of example only with reference to the accompanying drawings in which:

> Fig. 1 (a) and (b) are diagrammatic views of a positive displacement pump arrangement of the prior art;
>
> Figs. 2, 3 and 4 are diagrammatic views of a dispensing assembly according to the invention;

Figs. 5, 6 and 7 illustrate a particular embodiment of dispenser for three different positions of the separation membrane;

Figs. 8, 9 and 10 illustrate diagrammatically another alternative construction of the dispenser.

Fig. 11 illustrates another construction of dispenser.

Fig. 12 illustrates an alternative construction of dispensing assembly;

Fig. 13 illustrates another construction of dispensing assembly;

Figs. 14 and 15 illustrate two embodiments of the compression wave generator utilising piezo actuators;

Figs. 16 and 17 illustrate two other embodiments of compression wave generator utilising a magnetostrictive actuator;

Fig. 18 illustrates another embodiment of compression wave generator utilising a magnetic coil actuator;

Figs. 19 and 20 illustrate another embodiment of the dispenser in which the compression wave generator consisting of piezoelements is directly attached to the tip;

Fig. 21 illustrates a further construction of dispenser in which the compression wave generator consisting of a piezoactuator is attached to the nozzle;

Fig. 22 illustrates a further construction of the dispenser in which the compression wave generator comprises a magnetostrictive actuator attached to the nozzle;

Figs. 23a,b,c... illustrate embodiments of dispensing assembly according to the invention employing a pressure source and a high-speed valve;

Figs. 24 and 25 illustrate still further dispensers in which the compression wave generator consists of a magnetic coil actuator attached directly to the dispenser;

Fig. 27 illustrates a fragment of another dispensing assembly in which the drop off and droplet navigation are accomplished by charging electrode positioned underneath the target substrate;

Fig. 28 illustrates the means for drop off and electrostatic droplet navigation;

Fig. 29 illustrates another arrangement of electrodes that can be used for drop off and electrostatic droplet navigation;

Fig. 30 illustrates a multichannel dispenser capable of aspirating and dispensing a number of liquids simultaneously;

Fig. 31 illustrates yet another multichannel dispenser capable of aspirating and dispensing a number of liquids simultaneously;

Fig. 32 illustrates yet another dispensing assembly capable of aspirating and dispensing small volumes of liquids with high precision and also capable of aspirating and dispensing relatively large volumes of liquids.

Fig. 33 illustrates yet another dispensing assembly.

Referring to the drawings and initially to Figs. 1 (a) and (b) there is illustrated the prior art showing a conventional method of liquid droplet production using a positive displacement pump. There is illustrated a motor 1 driving a piston 2 of a positive displacement pump 3 containing a system liquid, namely, water 4 connected by

flexible tubing 5 to a robotic arm 6 carrying a nozzle 7 having a tip 8 into which the tubing 5 projects. A sample liquid 9 is contained in the nozzle 7 adjacent to the tip 8 and separated from the water 4 by a gas bubble 10 see Fig. 1 (b). The motor 1 which is usually a stepper or servo motor will each time move the piston 2 to dispense the sample liquid.

Referring to Fig. 2 there is illustrated dispensing assembly according to the invention. The dispensing assembly consists of a dispenser comprising an inner part 1 and a nozzle mounting part 2 of the dispenser. There is flexible elastomer membrane clamped between the part 1 and part 2 of the dispenser by means of the clamping means. The elastomer membrane hermetically divides the dispenser into two sections called system liquid reservoir and the sample liquid reservoir. The system liquid reservoir communicates with the syringe pump by means of a nonexpendable tubing. The syringe pump is controlled by a syringe pump motor that is in turn controlled by a controller. There is a nozzle that communicates with the sample liquid reservoir. The nozzle is inserted in the dispenser preferably in such a way that it does not protrude significantly inside the sample liquid reservoir. The inner surface of the sample liquid reservoir is preferably smooth. Fig. 2 also shows means for drop detachment from the nozzle. They consist of a conducting plate positioned underneath the substrate. High voltage source controlled by the controller generates electrostatic field between the tip of the nozzle and the substrate. Both the nozzle and the substrate are electrically connected to the high voltage source. In the embodiment shown in Fig. 2, parts 1 and 2 of the dispenser are clamped together tightly by means of clamping means. Alternatively, they could be bonded together e.g. by means of a glue.

In a typical embodiment, the flexible membrane is made of a material such as Latex with the thickness of some 0.1 to 0.5 mm. The nozzle is a stainless steel capillary with the internal diameter of 0.07 to 0.4 mm. In a typical embodiment the system liquid reservoir and sample liquid reservoir have axial symmetry. In the embodiment shown in Fig. 2, the axes of the system liquid volume and the sample liquid volume coincide with the axis of the nozzle, although other embodiments, in which this is not the case, can readily be designed. The walls of the sample liquid

reservoir are preferably smooth so that when the membrane is fully extended to expel the sample liquid from the dispenser, it applies tightly to the walls of the dispenser to reduce the dead volume in the dispenser. The smooth inner walls of the sample liquid reservoir also reduce the chances of making a puncture in the membrane. Typically the diameter of the sample liquid reservoir is some 0.4 to 4 mm and its depth is in the range of 0.4 to 4 mm although values outside this range can be used depending on the desired volume of dispensation. In a typical embodiment, parts 1 and 2 of the dispenser are formed out of plastic by injection moulding or another suitable mass production technique. The dispenser then becomes essentially a low-cost, disposable element.

The drop off electrode can also be used advantageously during the aspiration phase. At the end of the aspiration, when the nozzle is removed from the source of the sample liquid from which the sample liquid has been aspired, a drop of sample liquid may get attached to the tip of the nozzle. This drop is undesirable for many applications. The volume of this drop is difficult to control since it depends on the surface tension of the specific sample liquid aspired. This drop contributes to the wastage of valuable sample liquid and also can have a detrimental effect on the accuracy of the very first dispensation as it can add to the volume of the first dispensation. Therefore, the present invention proposes a device and method to avoid such a drop. After the aspiration, when the nozzle is removed from the source of the sample liquid (e.g. well plate with the sample liquid), a strong electric field is applied at the tip of the dispenser. This field removes any such droplet attached to the tip. The field is generated by means of a high voltage applied between the drop off electrode and the nozzle. This is also discussed in description of the figures below. It is proposed that in a typical application, the robotic arm removes nozzle of the dispenser from the sample well plate by only a some 1 to 5 mm in a vertical direction and then the voltage is applied to the drop off electrode to transfer sample liquid attached to the nozzle back exactly into the same well from which it has been aspired. This avoids unnecessary wastage of the sample liquid and reduces the risk of cross contamination.

Referring to Fig. 3, there is illustrated another dispenser. The only difference here

is that there is a pressure sensor attached to the system liquid reservoir. The readings from the pressure sensor are sent to the controller during the aspiration and dispensation. The prime purpose of the pressure sensor is to ensure that the membrane and other part of the system liquid reservoir are not destroyed by means of excess pressure produced by the syringe pump. During the dispensing, the pressure in the system liquid reservoir will gradually rise from the value essentially equal to the atmospheric pressure when the membrane is not bent, i.e. stretched straight. This increase above the atmospheric pressure is due to additional pressure resulting from the stretched membrane being bent into the sample liquid reservoir. Once the membrane is fully pressed against the wall of the sample liquid reservoir, the excess system liquid further expelled from the syringe pump cannot be accommodated by the dispenser any more and therefore the pressure in the system liquid reservoir will rise sharply if the syringe pump continues expelling the system liquid. To prevent destroying the membrane, tubing or syringe pump itself, the readings from the pressure sensor are continuously taken by the controller. The reading of pressure P_0 corresponding to the membrane being fully extended into the sample liquid reservoir could be recorded by the controller using e.g. calibration run of the dispenser. Then the threshold limit pressure P_{th} could be selected as e.g. $P_{th}=1.1*P_0$ or another suitable value marginally above the value of P_0. Thus if the pressure in the system reaches the value of P_{th}, the controller stops advancement of the syringe pump's plunger and discontinues expulsion of the system liquid from the pump. This would then indicate that the dispenser is empty of the sample liquid. Similarly during the aspiration, once the pressure in the system liquid reservoir has been reduced to the atmospheric pressure, the membrane is stretched straight. It could be beneficial to stop moving the plunger of the syringe at this moment. The pressure range at which the syringe pump should stop moving during the dispensing and aspiration of liquid can be selected depending on the specific configuration of the dispenser. In some instances it may be beneficial to operate the dispensing assembly in such a way that the membrane is continuously extended into the sample liquid reservoir. This is described in detail in relation to Fig. 30.

Referring to Fig. 4, there is illustrated a further dispensing assembly similar to that

of Fig. 3. The main difference between the dispensing assemblies shown in Figs. 3 and 4 is that there are valves 1, 2 and 3 in the latter embodiment. All the valves can be electrically opened and closed by the controller. Valve 1 separates the system liquid reservoir from the syringe pump. Valve 2 separates the system liquid reservoir from the system liquid supply. Valve 3 separates the system liquid supply from the outside atmosphere. System liquid supply is a container filled with a system liquid. This could be e.g. a flexible bag preferably with the volume greater than the volume of the system liquid reservoir communicating with the latter. Those skilled in the art can appreciate that by manipulating the valves 1, 2 and 3 and syringe pump one can fill in the system liquid reservoir with the liquid and expel any air bubbles from it. It is clear from the discussion above that it is preferable to expel bubbles of air/gas from the system liquid reservoir. Ones the system liquid reservoir is filled up with a system liquid, operation of the dispensing assembly is as is described above. Alternatively the system liquid supply could consist of an additional syringe or another syringe pump filled with system liquid. Process of filling the system liquid reservoir with the system liquid and expelling gas bubbles could be simplified if the system liquid supply indeed comprises a separate syringe pump.

Means for tight clamping of the parts 1 and 2 of the dispenser are not shown in Fig. 4. It is proposed that in this particular embodiment the two parts are bonded together with the membrane bonded in between. Clearly they can also be clamped by means of a spring or other suitable means.

In the embodiment shown in Fig. 4, the inner surface of the part 1 of the dispenser facing the membrane is not flat but convex.

Figs. 5 to 7 show dispenser for three different positions of the membrane. Fig. 5 shows the dispenser with membrane fully pressed against the part 1 of the dispenser. This corresponds to the dispenser having aspirated the maximum amount of sample liquid. Fig. 7 shows the dispenser with the membrane fully pressed against the part 2 of the dispenser. This position corresponds to the sample liquid being fully expelled from the dispenser. Fig. 6 corresponds to an

intermediate position of the membrane. It is important to appreciate that the membrane can move from the position shown in Fig. 5 to the one shown in Fig. 7 in a number of steps. For example the volume comprised between the parts 1 and 2 or the dispenser could be equal to some 2 microlitres and could be ejected in e.g. 100 steps making each dispensation equal to 20 nanolitres. It could also be ejected in one step. The membrane could be clamped between the parts 1 and 2 of the dispenser by means of clamping screws or other suitable means. In the embodiment shown in Figs. 5, 6, 7 there is a circular rim made at the part 2 of the dispenser to facilitate clamping of the membrane. In this particular embodiment the inner surface of the part 1 of the dispenser facing the membrane in concave.

Figs. 8 to 10 show another embodiment of the dispenser using an expandable bag. The expandable bag separates the system liquid reservoir from the sample liquid reservoir. Fig. 8 shows the expandable bag in an almost fully expanded position. Fig. 10 shows it in the fully compressed position when essentially all the sample liquid is being expelled. Fig. 9 shows the expandable bag in an intermediate position. The only sample liquid remaining in the dispenser shown in Fig. 10 is the liquid in the nozzle. To avoid cross contamination through the liquid remaining in the nozzle, the dispenser can aspirate and eject a washing liquid. In this case the sample liquid remaining in the nozzle will be diluted/washed out. If necessary, this procedure can be repeated several times before the dispenser is filled up with a new sample liquid. It can be advantageous to make the expandable bag of an elastomer with a significant range of elasticity. This would allow reducing the dead volume in the dispenser left inside the expandable bag at the end of the dispensation. In this particular embodiment the parts 1 and 2 of the dispenser are held together by means of glue or another suitable bonding agent.

Referring now to Fig. 11 there is illustrated an embodiment of the dispenser in which parts similar to the ones at the previous figures are indicated with the same numerals. The difference here is that there are two membranes: membrane 1 and membrane 2 instead of a single one. This embodiment allows removing part 2 of the dispenser from the part 1. Membrane 1 is bonded around the edge of the part 1 of the dispenser e.g. by gluing and preferably remains permanently attached to the

part 1 of the dispenser. In a similar manner the membrane 2 is bonded around the edge of the part 2 of the dispenser and remains permanently attached to the part 2 of the dispenser. There are also springs and clamping plates 1 and 2 that are clamping parts 1 and 2 of the dispenser tightly together. Clamping of the two parts of the dispenser could be accomplished by using other means that be readily proposed by those skilled in engineering graphics.

When changing from one sample liquid to another one, part 2 along with the membrane 2 that has been in contact with the sample liquid can be exchanged to avoid cross contamination. Part 1 along with the membrane 1 does not come in direct contact with the sample liquid at all. This embodiment makes effectively the dispenser a disposable element and removes the need to wash it when the sample liquid is exchanged. Essentially the disposable element is part 2 of the dispenser.

One could also design other arrangements employing more than two membranes.

It should be appreciated that for the embodiment with two membranes to function correctly, there should be no air/gas trapped in between the membranes 1 and 2. Therefore, the assembly of the dispenser and exchange of the disposable part 2 of the dispenser should be performed in such a manner as to avoid trapping the air bubble. A number of routines could be used to achieve this result. For example, just before the moment the two parts are finally tightly clamped and a small gap is left between them, the syringe pump could advance and press membrane 1 tightly against the membrane 2. This expels any air trapped in between the two membranes. Then the parts 1 and 2 of the dispenser are finally clamped with syringe pump in the same position. Other solutions can also be proposed to include pumping any air left from the area in between the two membranes. In Fig. 11 the two springs are only shown schematically not to complicate the figure and focus on the essential aspects.

Referring now to Fig. 12, there is illustrated an alternative dispensing assembly. The difference here is that the drop off electrode is located above the substrate. The drop off electrode is a metal ring. Equally it could be a conducting plate with a

hole or have another suitable geometry. The drop off electrode is connected to the high voltage source. In this particular embodiment the nozzle is connected to the ground potential. Strong electrostatic field is generated between the tip of the nozzle and the drop off electrode. This field pulls off the droplet from the tip of the nozzle.

Referring now to Fig. 13, there is illustrated a still further dispensing assembly. The main difference between the embodiments presented in Figs. 12 and 13 is that the latter comprises a compression wave generator. Compression wave generator is a device that can excite a wave in the system liquid and/or sample liquid that reaches the tip of the dispenser. The wave causes the drop suspended at the tip to detach from the dispenser. Therefore, the operation of the dispenser is as follows. Required volume of the sample liquid is expelled from the dispenser by advancing the plunger of the syringe pump. Then the compression wave generator is actuated by the controller and the drop is separated from the tip. In this embodiment the electrostatic drop off does not necessarily need to be used. However, incorporation of the electrostatic drop off electrode can still be advantageous even though the electrostatic field is not used for the droplet detachment. It could still be advantageous to apply a certain electrostatic field at the tip of the dispenser as this could be used to independently monitor the droplet separation from the tip e.g. by using Faraday pail. As the charge carried by the drop is related to its volume for a given value of the electrostatic field at the tip, measurement of the volume of dispensation can be performed. In addition, with the assistance of the electrostatic field, droplet separation using the compression wave generator is made more robust. In this case a rather strong electrostatic field. This field is not strong enough to pull off the droplet from the tip of the dispenser. However to a significant extent it compensates for the attraction of the drop to the tip caused by the surface tension. As a result, compression wave of smaller amplitude is sufficient to separate the drop from the tip.

Fig. 14 shows an embodiment of compression wave generator using a piezoactuator. In this particular embodiment the piezoactuator is based on a piezo tube. The thickness of the tube wall is some 0.3 to 0.8 mm. Its length is some 8 to

50 mm and diameter is 3 to 20 mm. Specific compression wave generators with values of wall thickness, length and diameter outside this range can also be readily designed. The tube is polarized radially. There are two metal electrodes on the piezo tube: one inside and the other one outside the tube. The piezo tube is rigidly coupled to the system liquid tube by means of the flange 1. Section of the system liquid tube in the compression wave generator could be made of a rigid material, e.g. it could be a thin wall metal tabulation. The other end of the section of the system liquid tube in the compression wave generator is closed with the flange 3. The other end of the piezo tube is closed by the flange 2. Flanges 2 and 3 are linked rigidly by a mechanical link, e.g. a metal spacer such as a section of a metal tabulation with the diameter of e.g. 2 mm and wall thickness of some 0.2 to 0.6 mm. The mechanical link is bonded to the flanges 2 and 3. Preferably the section of the system liquid tube between the flanges 1 and 3 has an expandable section that can extend the compress along the axis of the tube. The expandable section in Fig. 14 is a bellows. Other designs of compressible sections not in the form of a conventional bellows could be readily proposed by those skilled in the art of mechanical design. When a voltage is applied between the inner and outer electrodes, the thickness of the piezo tube changes. Therefore length of the radially polarized tube changes as well along with the distance between the flanges 1 and 3. The inner and outer electrodes are connected to a voltage pulse generator capable or generating a voltage pulse with the amplitude of some 100 to 500 V and the duration of 1 microsecond. By applying this pulse to the inner and outer electrodes, one therefore excites a wave in the system liquid. When choosing the amplitude of the voltage pulse applied to the inner and outer electrodes, one has to be careful not to exceed the maximum allowed value of the electric field that can depolarize the piezo tube. This depends mainly on the material of the tube, and its thickness and also one some other parameters such as e.g. temperature of the tube. Typical values for the depoling electric field are in the range of 300 to 600 V/mm.

The volume expelled from the compression wave generator as a result of the piezo tube contraction is proportional to the voltage applied to the piezo tube from the voltage pulse generator, length of the piezo tube and cross sectional area of the

bellows. This volume can be very small by comparison with the volume of the drop to be dispensed and still the compression wave generator could function correctly. Having the timing of the piezo tube contraction short is as important as increasing the amplitude of contraction. The piezo tube with the length of some 10mm typically contacts by up to some 5 micrometers. If the cross sectional area of the bellows is some 5 mm^2, then the volume expelled by the compression wave generator is only up to some 25 nanolitres. When choosing parameters of the compression wave generator, one should take into account expandability of the tubing joining the compression wave generator with the dispenser. We have assumed above that the tubing is unexpandable. In practice when the compression wave is launched, the tubing will expand to a certain extent and dampen the compression wave. The required amplitude of the compression wave also depends on the parameters such as surface tension of the liquid dispensed and diameter of the nozzle. In addition it depends on the distance between the compression wave generator and the tip. In general the longer this distance, the more significant is the damping of the compression wave by the time is reaches the tip. Calculating the exact amplitude of the compression wave is therefore unpractical or impossible. Practical way of choosing the amplitude of the compression wave is as follows. The voltage generated by the voltage pulse generator should be gradually increased launching the waves of progressively increasing amplitudes. The duration of the pulse generated by the voltage pulse generator should be kept as short as possible. For example, one could generate pulses with the duration of 1 microsecond and the amplitude of 20, 40, 60, 80 and so on Volt. One should simultaneously monitor if the drop separation has occurred. There is a critical voltage required for the drop separation that depends on a number of parameters of the dispenser as described above. One should set up the amplitude of the voltage pulse generator above the critical values for all the liquids to be handled by the dispenser. If the maximum voltage that can be applied to the piezo tube is still insufficient to cause the drop off, the length of the piezo tube or the cross sectional area of the bellows should be increased.

Fig. 15 shows another embodiment of the compression wave generator. The difference between the Figs. 14 and 15 is that the latter has an elastic compression

wave membrane instead of a rigid flange 3 at the end of the system liquid tube and also has no bellows. The shock wave membrane could be a thin metal foil, with a thickness of some 20 micron or greater bonded to the end of the system liquid tube. To increase the range of elasticity of the membrane, it could be advantageous to increase the diameter of the system liquid tube to over 10 mm. This would clearly require increasing the inner diameter of the piezo tube. In the embodiment shown in Fig. 15 there is a spring that spring loads the flange 2 against the compression wave membrane. In this embodiment the mechanical link is a bar with the diameter of some 1 to 2 mm mechanically coupling the centres of the compression wave membrane and flange 2. As bonding of the spring to a brittle piezo material can be complicated, there is an intermediate piezo tube support inserted between the piezo tube and the spring. It is essentially a metal ring or segment of a tube to which the spring is bonded and the piezo tube is glued/bonded. The other purpose of the piezo tube support is to increase the mass of the assembly attached to the spring. Increasing the mass can be advantageous for the following reason. One can appreciate that if the length of the piezo is decreased slowly as a result of a slow voltage ramp applied to the tube, this piezo tube's length reduction will be absorbed by extension of the spring's length and therefore will not be fully transferred into the compression wave membrane. However, if the contraction of the piezo tube happens very rapidly caused by a short voltage pulse applied to the piezo tube, the situation in different. In this case, most of the piezo tube's length contraction will be absorbed by the compression wave membrane provided the mass of the piezo tube and the piezo tube support is considerably greater than the mass of the flange 2 and the mechanical link. This result is then based on inertia. The inertia can be a major player during extension/contraction of the piezo tube caused by a short voltage pulse. Indeed although the compression of the piezo tube is relatively small and is typically in range of 10^{-6} to 10^{-5} m for the tube of some 10 mm length, the shortness of the time during which the extension takes place (10^{-7} to 10^{-5} sec) results in a significant value of the acceleration. Those skilled in the art can estimate that acceleration is in the range of 10^4 to 10^9 m/sec^2. Therefore, by using action of inertia, one can achieve the situation whereby the shock wave membrane is preloaded against the flange 2 by means of a relatively soft spring with significant range of elasticity. Yet,

this softness of the spring is not an obstacle during the rapid compression of the piezo tube caused by the voltage pulse applied to it.

Fig. 16 shows another embodiment of the compression wave generator. In this embodiment, the compression wave is actuated by means of four pillars of magnetostrictive material. There are magnetic field coils around each of the pillars. Two pillars with two coils are shown in Fig. 16. The pillars join the flanges 1 and 2. The diameter of the pillars is some 1 to 5 mm and their length is some 10 to 30 mm. Embodiments of compression wave generators with magnetostrictive elements having dimensions outside this range could be also designed. In the same way is in Fig. 14, there is mechanical link between flanges 2 and 3. Flange 1 is bonded to the system liquid tube. There is an expandable element in the system liquid tube between the flanges 1 and 3. In the embodiment shown in Fig. 16, this expandable element is bellows. Magnetic field coils are connected to the current pulse generator. The generator can generate a current pulse and therefore the pulse of magnetic field. As a result, the length of the magnetostrictive pillars will change moving the flange 2 and therefore coupling the compression wave into the system liquid through the mechanical link. The current pulse generator is controlled by the controller.

Numerous other designs employing magnetostrictive element/elements could be readily proposed. For example one could use a single cylindrical magnetostrictive element in the shape of a cylinder instead of a number of pillars. It is not necessary to use separate magnetic field coil of each of the pillars. One could generate field around all of the pillars using a single coil. Suitable magnetostrictive materials can be found in handbook on magnetic materials.

Fig. 17 shows another embodiment of the compression wave generator using a magnetostrictive actuator. Similarly to the embodiment shown in Fig. 15, there is no bellows and there is now a spring to preload the flange 2 against the compression wave membrane. Operation of this embodiment of compression wave generator is self- explanatory on the basis on the description related to Figs. 15 and 16.

Fig. 18 shows another embodiment of the compression wave generator. This is not the preferred option by comparison with the ones based on a pizoactuator or magnetostrictive actuator. The reason is that by comparison with the previous embodiments it enables slower movement of the shock wave membrane with greater amplitude. On the contrary, it can be beneficial to actuate the shock wave membrane with small amplitude but with a faster movement. In Fig. 18, parts identical to the ones shown in previous figures are indicated using the same numerals. There are two cores of magnetic material: magnetic cores 1 and 2. There are also coils 1a, 1b, 2a, 2b. Each of the two magnetic cores is cut into two parts forming two half-cores. There are springs inserted in between these. As the coils are energized with a magnetic field by means of a current pulse generator, there will be attractive force acting between the two parts of the magnetic cores. This force will push the flange 2 towards the compression wave membrane and will excite the compression wave in the system liquid. The coils 1a and 1b should excite magnetic field that is opposite to each other as indicated by arrows. The same applies to the coils 2a and 2b. In this way they excite continuous magnetic flux throughout each of the two magnetic cores. It may be beneficial to use the core of magnetic material having high magnetic permeability at high frequency. The reason is that the short current pulse in the coils has high-frequency components in the spectrum. Therefore, to increase the force of attraction of the two parts of magnetic core, it is advantageous to use the core with high magnetic permeability at high frequency. Suitable materials can be found in numerous product data books.

Figs. 19 and 20 show an embodiment of the dispenser in which the compression wave generator effectively forms part 1 of the dispenser. The part 1 of the dispenser comprises a bimorph piezo. The bimorph piezo consists of two or more layers of piezo material. The two layers in Figs. 19 and 20 are piezo layer 1 and piezo layer 2. They are polarized in such a way that when one of the layers extends, the other one contracts. For example, suppose the upper of the two layers extends and the lower one contracts. In this case the central area of the part 1 of the dispenser bends towards the membrane as shown in Fig. 20. If this is done

rapidly as a result of a voltage pulse applied to the piezo bimorph, the compression wave is excited in the dispenser. There are three electrodes connected to the bimorph piezo. The electrodes are connected to the voltage pulse generator. One should keep in mind that bending mode of mechanical oscillations usually has lower resonance frequency than the compression mode. Therefore, even if the voltage pulse generator sends a very short voltage pulse to the piezo layers, the bimorph may not be able to respond by a rapid deformation if its own resonance frequency is too low. This should be taken into account when the thickness of the piezo bimorph is determined. By increasing the thickness of the bimorph or by decreasing its length, one can increase the resonance frequency of the compression waver generator. The shape of the piezo bimorph under the bending deformations can be calculated using the standard formulas for the mechanics of deformations readily available in the literature. Parts 1 and 2 of the dispenser can be bound together in a manner similar to the one described in earlier embodiments. The thickness of the layers depends on the size of the dispenser that is in turn determined by the required volume of the sample liquid reservoir. For a sample liquid reservoir with the diameter of some 5 mm, the thickness of the piezo layers in the range of 0.2 to 0.6 mm was found to be acceptable. The thicker the individual layers of the bimorph, the smaller is the bending deformation. Therefore, when thicker layers are used, a voltage pulse of greater amplitude should be applied to the bimorph to excite the wave of the same amplitude. On the other hand using thicker piezo bimorph has advantage in that the resonance frequency of the bimorph increases making excitation of a faster compression wave possible.

One should note that the deformation of the bimorph is shown greatly exaggerated in Fig. 20 to make reading of the figure easier.

Referring now to Fig. 21 there is illustrated another embodiment of dispenser. Parts identical to the ones presented in previous figures are indicated with the same numerals. In this embodiment the compression wave generator based on a piezo tube is coupled to the nozzle. It can be advantageous to make the nozzle of a capillary with a very thin wall to enable its easier extension/contraction by means of the compression wave generator. The piezo tube is bonded between flanges 1 and

2. The two flanges are in turn bonded to the nozzle. The piezo tube is polarized radially in the same was in the embodiment presented in Fig. 14. The length of the tube is some 5 to 30 mm and its inner diameter is some 1 mm or greater. The wall thickness of the tube is some 0.3 to 1mm. Compression wave generators using tubes with sizes outside this range can also be readily designed. There are two conducting electrodes on the tube: the inner and the outer one. When the voltage is applied between the two electrodes, the thickness of the piezo tube is changed. Therefore its length also changes and this moves flange 2 with respect to the flange 1. If the voltage is applied in the form of a short pulse, the drop can become detached from the tip of the nozzle. All the issues related to the maximum value of the voltage than can be safely applied between the two electrodes of the tube without causing its depoling, also apply in this embodiment.

Referring now to Fig. 22, there is illustrated another embodiment of dispenser in which parts similar to the ones shown in previous figures are indicated with the same numerals. In this latter embodiment the compression wave generator is coupled into the nozzle of the dispenser. The compression wave generator uses an actuator of magnetostrictive material. The cylinder (or a number of bars) of magnetostrictive material is bonded between two flanges, 1 and 2 which are in turn bonded to the nozzle as shown in Fig. 22. The outer diameter of the cylinder could be in the range of some 1 to 5 mm. Length of the cylinder could be in the range of some 10 to 30 mm. The cylinder of the magnetostrictive material is placed inside a coil. The coil is connected to the current pulse generator. When the coil is energised by the current pulse, it generates a pulse of magnetic field around the cylinder of the magnetostrictive material. The current pulse generator is controlled by the controller. Operation of the compression wave generator is as follows: a short current pulse in the coil generates the pulse of magnetic field at the cylinder of magnetostrictive material and causes the compression of the cylinder. The nozzle is also rapidly compressed thus enabling the separation of the drop from the tip of the nozzle.

In both embodiments shown in Figs. 21 and 22, the care should be taken to reduce the mass of the flanges 1 and 2. Increasing their mass increases inertia of the

compression wave generator and decreases amplitude of the wave.

Referring now to Fig. 23a there is illustrated a dispensing assembly in which parts similar to the ones presented in the previous figures are indicated using the same numerals. In this case the essential new elements in the dispensing assembly are the high-speed valve and a pressure source. The pressure source could be e.g. a compressor capable of creating positive pressure in the range of up to some 10 to 20 Bar. Alternatively it could be a bottle of compressed gas. Pressure sources with other values of pressure could also be used depending on the specific design of the dispenser. The high-speed valve is connected to the system liquid reservoir as shown in Fig. . Both, the high-speed valve and the pressure source are controlled by the controller. Operation of this dispensing assembly is as follows. Suppose, the system liquid continuously fills up the line joining the high-speed valve with the tubing and also the high-speed valve itself. In this case the level of system liquid is above the high-speed valve as shown in Fig. 23a. Suppose, the high-speed valve is closed and pressure in the line above the high-speed valve, i.e. in the section of the line joining the high-speed valve with the pressure source, is equal to P_{eject} that is above the atmospheric pressure. Suppose the sample liquid is aspirated into the ~~sample liquid reservoir by displacing the syringe plunger as described above. The~~ volume of the sample liquid aspirated is defined by the displacement of the syringe pump. To eject the entire volume of the sample liquid from the sample liquid reservoir, the high-speed valve is opened. Pressure in the system liquid reservoir will rise rapidly and as a result the membrane will be deformed to eject all the sample liquid from the sample liquid reservoir. The optimal pressure P_{eject} depends on the specific dimensions of the dispenser. Primarily it depends on the length and the diameter of the nozzle. The greater the length and the smaller is the diameter, the greater is the pressure required to ensure that the sample liquid expelled from the sample liquid reservoir gets detached from the tip. On the other hand the pressure should not be too great to avoid damage to the membrane and also for the reason that some biological liquids should not be subjected to an excessive pressure. We have found that the pressure in the range of up to 5 Bar is often adequate for the dispensation in the range of down some 10 nl. In some cases, especially when dispensing liquids with higher viscosity such as e.g. glycerol,

greater pressure in the range of 10 to 30 Bar can be preferable.

Fig. 23b shows another embodiment of the dispensing assembly. The difference between the embodiments of Figs. 23a and 23b is that the latter has additional valves 4 and 5 and means for monitoring the level of system liquid in the control line between the high-speed valve and pressure source. The valve 4 is installed in the control line between the high-speed valve and the pressure source and it can isolate the control line from the pressure source. Valve 5 is a release valve and it serves to release pressure from the control line as it can be opened to the atmosphere. The means for monitoring level of liquid in the control line consist of a laser diode and a photodiode. The laser diode focuses a laser beam on the control line, and the photodiode receives the light that has passed through the control line. As the level of liquid passes through the focused laser beam, the signal received by the photodiode changes. The photodiode and the laser diode are connected to their respective control circuits that are not shown in Fig. 23b in order not to take attention from essential points. Those skilled in the art can readily propose numerous other means for control of level of system liquid including in the control line optical and non-optical means. Those skilled in the art can further appreciate that if optical means of the level control are employed then the control line should be preferably optically transparent. They can further appreciate that to improve signal to noise ratio and therefore accuracy of the monitoring of the level of liquid it may be advantageous to modulate light emitted by the laser diode. This would allow using a phase-sensitive detector (lock-in amplifier) or narrow-band amplifier to measure signal from the photodiode. It can be further proposed that the system liquid is dyed with an ink to improve sensitivity of monitoring of the level of liquid. From the above one can appreciate that the system liquid extends continuously from the tubing into the tubing 2, high-speed valve and terminates at the level of liquid high.

The dispensing assembly operates as follows. The level of liquid in the control line is maintained constant at certain stages of the aspirate-dispense cycle. All the walls of the control line and tubing 2 joining the high speed- valve and the tubing are nonexpendable. If one considers that the liquid up to the height of the level of liquid

in the control line also makes a part of the system liquid reservoir, then it is clear that all the above analysis of the dispensing assembly applies here. Suppose, the high speed-valve is closed and the syringe plunges pulled back by the volume V_{asp} to aspirate system liquid. Suppose level of liquid in the control line is equal to l_0 . To dispense the system liquid, first the valve 5 and the high-speed valve are kept closed. Valve 4 is open. Then the control line is pressurised. When the high-speed valve is open, the sample liquid is expelled from the dispenser as explained in the text related to Fig. 23a. To aspirate the liquid, the valve 4 closes and high-speed valves opens. The valve 5 is open preferably in short intervals/pulses so that level of liquid in the control line becomes equal to the same value l_0. Then the high-speed control valve is closed, the syringe plunger is slowly moved forward to expel the volume V_{asp} it has aspirated in the previous aspiration cycle and therefore all the elements in the dispensing assembly have returned to their initial position and the dispensing assembly can again aspirate the sample liquid as described above.

Fig. 23c shows an embodiment incorporating a membrane in the tubing 2.

Referring now to Fig. 24 there is illustrated a still further dispenser. In this embodiment the compression wave generator consists of a hammer connected to a magnetic actuator. Direction of the movement of the hammer is shown by arrows. The hammer can move on the pivotal point as shown. The magnetic actuator comprises a coil coupled by magnetic field to a soft magnetic core. There is also a preloading spring pulling the hammer up so that in the absence of current in the coil, the hammer is pulled away from the part 1 of the dispenser. If the coil is energised by a current pulse, there is a force pulling the soft magnetic core into the coil. As a result, the hammer accelerates and hits the part 1 of the dispenser thus exciting a compression wave. There is also a stopper limiting movement of the hammer. In the absence of the current in the coil, the hammer rests on the stopper. The amplitude of the movement of the hammer depends on the specific design of hammer and the magnetic actuator. It may be advantageous to limit movement of the hammer in such a way that it cannot travel more than some 1 to 3 mm between the two positions: one with the hammer resting on the part 1 of the dispenser and the one with the hammer resting on the stopper. The parts 1 and 2 of the dispenser

are held together by means as described above, e.g. by bonding or spring loading. In this embodiment it is crucially important to shorten the duration of the current pulse applied to the coil. In fact the pulse could re relatively long to cause significant acceleration of the hammer.

Fig. 25 shows another embodiment of the compression wave generator that is also based on a magnetic actuator. There is a core of material with high magnetic permeability that consists of two parts: part 1 and part 2 of the core. They can move on a swivel joint with respect to each other to open and close the core gap. Part 2 of the core is rigidly attached to the part 1 of the dispenser. There is a coil placed around parts 1 and/or 2 of the core. In the embodiment shown in Fig. 25, the coil is placed around part 1 of the core. The coil is connected to the current pulse generator that is in turn controlled by a controller. There is a spring inserted in such a way that the two parts of the core are separated by a core gap of up to some several millimetres when no current is driven through the coil. When the coil is energised by a current pulse, the two parts of the magnetic core attract each other and if the current is sufficiently strong, the core gap will close. Therefore, part 1 of the core will knock on the part 1 of the dispenser thus exciting the compression wave.

Referring now to Fig. 26 there is illustrated a dispensing assembly indicated generally by the reference numeral 120 incorporating a dispenser 40 as described above. In this embodiment the droplets are identified by the numeral 58 and successive subscripts thus 58(a) to 58 (c). The dispensing tip 46 effectively forms or incorporates an electrode by virtue of being grounded by the earth line 59. There is mounted below the dispenser 40 a receiving substrate 121 incorporating reagent wells 122. For three of the wells 122 a, b and c there are, for simplicity identified by the same subscript letters, droplets 58 a, b and c both approaching the wells 122 and in them. Positioned below the receiving substrate 121 is a drop off electrode 123 in turn mounted on an indexing table 124. The drop off electrode 123 is connected to a high voltage source 125.

The indexing table 124 is used to position the drop off electrode 123 below the

appropriate reagent well 122 as shown by the interrupted lines in the drawing.

Referring now to Fig. 27 there is illustrated an alternative construction of dispensing assembly, indicated generally by the reference numeral 130 in which parts similar to those described in Fig. 26 are identified by the same reference numerals. In this embodiment there is provided a plurality of drop off electrodes 131 on the indexing table 124, which are individually connected to the high voltage source 125.

Referring now to Fig. 28 there is illustrated still further construction of dispensing assembly indicated generally by the reference numeral 140 in which parts similar to those described with reference to Fig. 27 are identified by the same reference numerals. In this embodiment there are provided additional deflecting electrodes 141 and 142. It will be appreciated that depending on the voltage on the deflecting electrodes 141 and 142, the droplets 58 will in conjunction with the drop off electrodes 123 navigate into the appropriate reagent well 122. This is illustrated clearly in Fig. 28 by the interrupted lines. In Fig. 28 there is also shown a drop off electrode 123 but it will be appreciated that such a drop off electrode 123 will not always be necessary. It is also possible to use a conducting plate such as illustrated in Fig. 3 or it is possible to use only deflecting electrodes. However, what will be appreciated by consideration of the dispensing assemblies as illustrated in Figs. 26 to 28 inclusive is that electrostatic navigation of the drops by means of both the drop off electrodes and the deflecting electrodes can be relatively easily achieved. For example, the drop off electrode could be in the form of a plate having at least one hole to allow a droplet pass therethrough.

With a further miniaturisation of the substrate targets, it becomes increasingly difficult to ensure that the drop reaches the correct destination as it is ejected from a liquid handling system. For applications such as high-density arrays, the size between the subsequent drops covering the substrate, herein called pitch, could be as small as 0.1 mm. In this invention there are two different means of controlling the destination of the drop, both are based on the electrostatic forces acting on the drop as it travels between the nozzle and the well.

Referring to Fig. 29 there is illustrated a test assembly indicated generally by the reference numeral 150 incorporating a dispensing assembly as illustrated in Fig. 4 and 8. There is provided a substrate 151 below which is mounted a pair of receiving electrodes in the form of plates 152 and 153 which in turn are connected to an electrical circuit indicated generally by the reference numeral 154 incorporating a high voltage supply 155 of approximately 5 KV. The separation between the dispensing tip and the substrate 151 was 15 mm. Tests were carried out.

The first way is to generate the electrostatic field with a small charged drop off electrode positioned underneath the well instead of a large conducting plate. The size of the electrode is smaller than the size of the well for accurate navigation. It may be advantageous as described above to have the drop off electrode in the shape of a tip to produce the strongest electric field at the centre of a destination well. The electrode produces a strong electric field underneath the well attracting the drop to the required destination position (usually the centre of the well). The drop off electrode may be attached to an arm of a positioner capable of moving it underneath the well plate and pointing to the correct destination well. Alternatively, the sample well plate may be repositioned above the drop off electrode in order to target a different well. It may be necessary to move the dispensing tip and drop off electrode synchronously. It may be advantageous to have a module with a number of drop off electrodes that could be connected to the high voltage supply independently. The distance between the electrodes could be the same as the distance between the centres of the wells in a well plate. In this case the drops could be navigated to different wells without actually moving the dispenser or the drop off electrode.

In an arrangement described above deflection electrodes are positioned along the path between the nozzle and the destination well. The electrodes are charged by means of a high voltage applied to them. As the drops leaving the dispensing tip are charged by the voltage between the dispensing tip and the drop off electrode, they will be deflected by the deflection electrodes.

It is important to realise that during the electrostatic drop off, the electrostatic force acting on the drop could much greater than the gravity force. In this case as the drop flies between the nozzle and the substrate, the direction of the path is determined by the direction of the electrostatic field.

While it is explained above in many instances necessary to calibrate the dispenser for each new liquid because the volume dispensed depends on the properties of the liquid and of the nozzle, in certain instances this is not required as has been explained above.

In the present invention we also envisage, as described above, the monitoring of the droplet in flight. It is important in many instances to be absolutely certain that the droplet was actually dispensed and ideally also to ascertain the volume of the droplet and this has been described in considerable detail above. Also it must be noted that the present invention proposes a method for the direct measurements of volume of the droplet which is not based on the detection or the timing of the drop-off but on direct measurement of the charge on the droplet.

Fig. 30 shows an embodiment of a dispensing assembly in which a number of different liquids can be aspirated and dispensed by means of single syringe pump. The most likely application of this device is simultaneous aspiration and dispensing of equal amounts of a number of liquids without intermixing. For example, it can be necessary to aspirate 48, 96, 384, 1536 or another number of liquids from a well plate and dispense these onto a target substrate or another well plate or a microchannel structure.

All the system liquid reservoirs of the dispensers are hydraulically connected to the syringe pump. If all the membranes in the separate dispensers are identical, the volume of the system liquid expelled by the syringe pump will be divided equally between the individual dispensers. For example if the volume of the system liquid expelled by the syringe pump is 960 nl and there are 96 dispensers in the assembly, the volume of the sample liquid expelled from each of the dispensers if

10 nl. If the membranes are not identical, then volume expelled from a dispenser with a softer, more elastic membrane is greater than the one expelled from a dispenser with stiffer membrane. In the embodiment shown in Fig. 30, there are electrostatic drop off electrodes positioned in the vicinity of the tips of the dispensers. The drops are detached from the nozzles by means of electrostatic field as these drop off electrodes are connected to the high voltage source. In the embodiment shown in Fig. 30, the drop off electrodes are connected to the high voltage source through a multiplexor unit so that individual drop off electrodes can be connected to high voltage source separately if required to detach droplets from the selected dispensers. Individual control of the voltage for separate dispensers is necessary for individual control of the dispensers. For example, for some applications it may be necessary to dispense liquid from all even-numbered dispensers into one well plate and dispense liquid from all the odd-numbered dispensers into another well plate.

For detachment of droplets from the tips, the dispensing assembly can employ a compression wave generator or pressure source as described in above embodiments.

In order to have equal volumes of sample liquid expelled from the individual dispensers, it is advantageous to have the membranes substantially pre-stretched during the entire dispensing step. The reason is that even if the membranes are identical, the volume expelled by the syringe pump may not be equally divided between the dispensers if the membranes are loose. It is desirable that identical additional extension of the membranes results in identical pressure increase in the individual dispensers. It is therefore advantageous to operate the assembly at a considerable excess pressure above the atmospheric pressure. The simplest solution can be to ensure that during the aspiration, the membrane is not allowed to become flat and remains always considerably bent towards part 2 of the dispenser.

One could readily design a dispenser in which the membranes at different dispensers are not identical. For example, one could design a dispenser in which the membranes on all the odd channels are twice stiffer than the ones of the even

channels. This dispenser could be used for application whereby it is necessary to dispense unequal amounts of liquids or dispense only liquids from some dispensers.

It is important to appreciate that a dispensing assembly in which individual dispensers are controlled by means of individual syringes, can also be designed. This can offer greater flexibility in the control of the individual dispensers that may be of benefit for certain applications.

Fig. 31 shows another embodiment of the dispenser in which instead of a membrane clamped between parts 1 and 2 of the dispenser, there are flexible elastomer bells separating the sample liquid reservoir from the system liquid reservoir. The bells are compressed by the pressure in the system liquid reservoir and expel sample liquid from the sample liquid reservoir. Once again the principle of the dispensing assembly is based on the fact that although the bells are made of an elastic material and will deform considerably during the dispensation, the volume of the bells will remain substantially unchanged. The embodiment of Fig. 31 shows a dispensing assembly with four channels. It is clear that dispensing assemblies with other numbers of dispensers can also be designed. Parts 1 and 2 of the dispenser are held together by any of the means as described above. The means for drop detachment from the end of the nozzles are not shown in Fig. 31. These could be similar to any of the means described above.

Fig. 32 shows another embodiment of the dispenser in which parts similar to the ones in the previous figures are indicated using the same numerals. In this embodiment there are two syringes: syringe 1 and syringe 2. Syringe 1 is a small volume syringe and it is used for accurate dispensing of small volumes. Syringe 2 is a larger volume syringe. It is used to achieve a large dynamic range. The two syringes can operate in a co-ordinated manner to achieve both a large dynamic range and high precision for dispensing small volumes.

Fig. 33 shows another embodiment of the dispensing assembly in which there are no nozzle capillaries attached to the part 2 of the dispenser. In this embodiment

there is an electrode positioned on the part 2 of the dispenser in such a manner that the sample liquid in the individual channels can be connected to the required potential. In the embodiment shown in Fig. 33, this electrode is connected to the ground potential. There are also drop off electrodes positioned in the vicinity of the individual dispensers. Other arrangements of electrodes can also be implemented. Clearly other means for drop detachment as described above such as compression wave generator and pressure source, can also be used.

In the specification the terms "comprise, comprises, comprised and comprising" or any variation thereof and the terms "include, includes, included and including" or any variation thereof are considered to be totally interchangeable and they should all be afforded the widest possible interpretation and vice versa.

The invention is not limited to the embodiment hereinbefore described, but may be varied in both construction and detail within the scope of the claims.

CLAIMS

1. A dispensing assembly for sample liquid droplets of less than 5 μl in volume comprising:-

   a dispenser body having a main bore;

   a nozzle mounted on the dispenser body and terminating in a dispensing tip, the nozzle having a nozzle bore with a nozzle entrance communicating with the main bore;

   a divider barrier for separating system and sample liquid within the assembly, the divider barrier comprising a body of elastomeric substantially incompressible material; and

   a positive displacement pump for delivery of metered quantities of system liquid through the assembly to expand the barrier to deliver sample liquid through the nozzle bore.

2. A dispensing assembly as claimed in claim 1, comprising:-

   a compression wave generator; and

   a controller having means to actuate the generator to cause a wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

3. A dispensing assembly as claimed in claim 1, comprising:-

   a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

4. A dispensing assembly as claimed in claim 1, in which the divider barrier is housed in the main bore dividing it into a system liquid portion and a sample liquid portion.

5. A dispensing assembly as claimed in claim 4, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

6. A dispensing assembly as claimed in claim 4, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

7. A dispensing assembly as claimed in claim 4, comprising:-

a magnetostrictive actuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence

causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

8. A dispensing assembly as claimed in claim 1, in which the dispenser body comprises a two part body, namely an inner part and a nozzle mounting part, housing respectively a system liquid portion and a sample liquid portion forming the main bore, means for mounting the divider barrier between the two parts and means for releasably connecting the two portions together.

9. A dispensing assembly as claimed in claim 8, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

10. A dispensing assembly as claimed in claim 8, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

11. A dispensing assembly as claimed in claim 8, comprising:-

a magnetostrictive actuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

12. A dispensing assembly as claimed in claim 8, in which the nozzle mounting part and divider barrier form the one sealed sub-assembly.

13. A dispensing assembly as claimed in claim 8, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

14. A dispensing assembly as claimed in claim 8, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

15. A dispensing assembly as claimed in claim 1, in which the dispenser body

houses the divider barrier therein and the dimensions of the divider barrier and the main bore are such that the system liquid can cause the divider barrier to lie against all of the main bore between the barrier and the nozzle entrance.

16. A dispensing assembly as claimed in claim 15, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

17. A dispensing assembly as claimed in claim 15, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

18. A dispensing assembly as claimed in claim 15, comprising:-

a magnetostrictive actuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

19. A dispensing assembly as claimed in claim 15, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

20. A dispensing assembly as claimed in claim 15, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

21. A dispensing assembly as claimed in claim 1, in which the dispenser body comprises:-

an inner part having a system liquid portion forming some of the main bore;

a nozzle mounting part having a sample liquid portion forming the rest of the main bore; and

means for releasably connecting the two parts together with the divider barrier sandwiched therebetween, the dimensions of the divider barrier and the main bore being such as to fit closely together in the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

22. A dispensing assembly as claimed in claim 21, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

23. A dispensing assembly as claimed in claim 21, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

24. A dispensing assembly as claimed in claim 21, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

25. A dispensing assembly as claimed in claim 1, in which the dispenser body comprises:-

an inner part having a system liquid portion forming some of the main bore;

a nozzle mounting part having a sample liquid portion forming the remainder of the main bore, the sample liquid portion adjacent the nozzle entrance being concave;

means for releasably connecting the two parts together with the

divider barrier sandwiched therebetween, the dimensions of the divider barrier and the main bore being such as to fit closely together in the main bore of the sample liquid portion and across and adjacent the nozzle entrance under the influence of the system liquid.

26. A dispensing assembly as claimed in claim 25, in which the mounting part, divider barrier and nozzle form the one sealed sub-assembly.

27. A dispensing assembly as claimed in claim 25, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

28. A dispensing assembly as claimed in claim 25, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

29. A dispensing assembly as claimed in claim 25, comprising:-

a magnetostrictive actuator for causing a sudden compression of

portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

30. A dispensing assembly as claimed in claim 1, in which the dispenser body comprises:-

an inner part having a system liquid portion forming some of the main bore;

a nozzle mounting part having a sample liquid portion forming the remainder of the main bore;

a divider barrier comprising a pair of closely contacting members, one member secured to the inner part and the other member to the nozzle mounting part; and

means for releasably connecting the parts together.

31. A dispensing assembly as claimed in claim 30, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a compression wave in the sample liquid as the positive displacement

pump completes delivery of the sample liquid to the dispensing tip.

32. A dispensing assembly as claimed in claim 30, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

33. A dispensing assembly as claimed in claim 30, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

34. A dispensing assembly as claimed in claim 1, in which the divider barrier is formed from a separate sample liquid container mounted in the dispenser body and connected directly to the nozzle entrance.

35. A dispensing assembly as claimed in claim 34, in which the dispenser body mounts a plurality of nozzles and a separate sample liquid container connected to each nozzle.

36. A dispensing assembly as claimed in claim 34, in which the dispenser body mounts a plurality of nozzles and a separate sample liquid container is connected to each nozzle, the liquid containers being so formed that there are at least two sets of individual divider barriers having different elastomeric properties.

37. A dispensing assembly as claimed in claim 34, in which the sample liquid container and nozzle form the one sub-assembly releasably connected to the dispenser body.

38. A dispensing assembly as claimed in claim 1, in which the divider barrier is

formed from a separate sample liquid container mounted in the dispenser body and the external dimensions of the divider barrier and the main bore being such as to fit closely together in the main bore across and against the nozzle entrance under the influence of the system liquid.

39. A dispensing assembly as claimed in claim 38, in which the dispenser body mounts a plurality of nozzles and a separate sample liquid container connected to each nozzle.

40. A dispensing assembly as claimed in claim 38, in which the dispenser body mounts a plurality of nozzles and a separate sample liquid container is connected to each nozzle, the liquid containers being so formed that there are at least two sets of individual divider barriers having different elastomeric properties.

41. A dispensing assembly for sample liquid droplets of less than 5 µl in volume comprising:-

a dispenser body having a main bore;

a divider barrier for separating the main bore into a system liquid portion and a sample liquid portion and comprising a body of elastomeric substantially incompressible material;

a nozzle mounted on the dispenser body and terminating in a dispensing tip, the nozzle having a nozzle bore with a nozzle entrance communicating with the sample liquid portion; and

a positive displacement pump for delivery of metered quantities of system liquid through the assembly to cause the divider barrier to move into and out of the sample liquid portion.

42. A dispensing assembly as claimed in claim 41, in which the dispenser body

is a two part body such that the sample liquid portion, divider barrier and nozzle form the one sealed sub-assembly.

43. A dispensing assembly as claimed in claim 41, in which the dimensions of the divider barrier and the main bore are such that the system liquid can cause the divider barrier to lie against all of the main bore between the barrier and the nozzle entrance.

44. A dispensing assembly as claimed in claim 41, in which the dispenser body comprises a two part body housing respectively a system liquid portion and a sample liquid portion forming the main bore with the divider barrier sandwiched therebetween, the external shape of the divider barrier being such as to fit closely in the main bore of the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

45. A dispensing assembly as claimed in claim 41, in which the external dimensions of the barrier and the main bore are such as to fit closely together in the main bore of the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

46. A dispensing assembly as claimed in claim 41, comprising:-

> a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and
>
> a controller having means to actuate the generator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

47. A dispensing assembly as claimed in claim 41, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing the compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

48. A dispensing assembly as claimed in claim 41, comprising:-

a magnetostrictive actuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause the compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

49. A dispensing assembly as claimed in claim 41, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

50. A dispensing assembly as claimed in claim 41, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

51. A dispensing assembly for sample liquid droplets of less than 5 µl in volume comprising:-

a dispenser body comprising a two-part dispenser body releasably connected together and having a main bore;

a divider barrier for separating the main bore into a system liquid portion and a sample liquid portion and comprising a body of elastomeric substantially incompressible material;

a nozzle mounted on the dispenser body and terminating in a dispensing tip, the nozzle having a nozzle bore with a nozzle entrance communicating with the sample liquid portion;

a positive displacement pump for delivery of metered quantities of system liquid through the assembly to cause the divider barrier move into and out of the sample liquid portion.

52. A dispensing assembly as claimed in claim 51, in which the sample liquid portion, divider barrier and nozzle form the one sealed sub-assembly.

53. A dispensing assembly as claimed in claim 51, in which the dimensions of the divider barrier are such that the system liquid can cause the divider barrier to lie against all of the main bore between the barrier and the nozzle entrance.

54. A dispensing assembly as claimed in claim 51, in which the dispenser body comprises a connector for releasably joining the two portions together with the divider barrier sandwiched therebetween, the dimensions of the divider barrier and the main bore being such as to fit closely together in the main bore of the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

55. A dispensing assembly as claimed in claim 51, in which the dimensions of the barrier and the main bore are such as to fit closely together in the main bore of the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

56. A dispensing assembly as claimed in claim 51, in which the divider barrier comprises:-

a pair of closely contacting membranes, one membrane secured to the system liquid portion and the other membrane to the sample liquid portion, and

means for releasably connecting the portions together.

57. A dispensing assembly as claimed in claim 51, comprising:-

a compression wave generator for causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to actuate the generator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

58. A dispensing assembly as claimed in claim 51, comprising:-

a piezoactuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing a compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the piezoactuator to cause the

compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

59. A dispensing assembly as claimed in claim 51, comprising:-

a magnetostrictive actuator for causing a sudden compression of portion of the assembly carrying the system liquid and hence causing the compression wave to be generated in the system liquid for transfer through the divider barrier and hence into the sample liquid; and

a controller having means to operate the magnetostrictive actuator to cause a compression wave in the sample liquid as the positive displacement pump completes delivery of the sample liquid to the dispensing tip.

60. A dispensing assembly as claimed in claim 51, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

61. A dispensing assembly as claimed in claim 51, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

62. A dispensing assembly as claimed in claim 1, in which the positive displacement pump comprises an assembly of at least two pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump.

63. A dispensing assembly as claimed in claim 41, in which the positive displacement pump comprises an assembly of at least two pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump.

64. A dispensing assembly as claimed in claim 51, in which the positive displacement pump comprises an assembly of at least two pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump.

65. A dispensing assembly as claimed in claim 1, comprising:-

at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump;

a two part body forming the dispenser body, namely an inner part and a nozzle mounting part, housing respectively a system liquid portion and a sample liquid portion forming the main bore;

means for mounting the divider barrier between the two parts;

means for releasably connecting the two portions together;

a plurality of nozzles in the mounting part; and

the divider barrier additionally separating portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

66. A dispensing assembly as claimed in claim 1, comprising:-

at least two positive displacement pumps connected in parallel, one

pump having a working stroke displacing a volume at least ten times larger than that of the other pump;

a two part body forming the dispenser body, namely an inner part and a nozzle mounting part, housing respectively a system liquid portion and a sample liquid portion forming the main bore;

means for mounting the divider barrier between the two parts;

means for releasably connecting the two portions together;

a plurality of nozzles in the mounting part; and

the divider barrier additionally separating portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

67. A dispensing assembly as claimed in claim 1, comprising:-

at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump;

a two part body forming the dispenser body, namely an inner part and a nozzle mounting part, housing respectively a system liquid portion and a sample liquid portion forming the main bore;

means for mounting the divider barrier between the two parts;

means for releasably connecting the two portions together;

a plurality of nozzles in the mounting part; and

the dimensions of the divider barrier and the main bore being such as to fit closely in the sample liquid portion and across and against the nozzle entrance under the influence of the system liquid.

68. A dispensing assembly as claimed in claim 30, comprising at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

69. A dispensing assembly as claimed in claim 30, comprising at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

70. A dispensing assembly as claimed in claim 38, comprising at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and a separate sample liquid container is connected to each nozzle, the liquid containers being so formed such that there are at least two sets of individual divider barriers having different elastomeric properties.

71. A dispensing assembly as claimed in claim 41, comprising at least two

positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

72. A dispensing assembly as claimed in claim 51, comprising at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion.

73. A dispensing assembly as claimed in claim 51, comprising at least two positive displacement pumps connected in parallel, one pump having a working stroke displacing a volume at least ten times larger than that of the other pump, the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties.

74. A dispensing assembly as claimed in claim 1, in which the dispenser body comprises:-

> an inner part having a system liquid portion forming some of the main bore;
>
> a nozzle mounting part having a sample liquid portion forming the remainder of the main bore;

a divider barrier comprising at least three closely contacting members at least one member being secured to each of the parts.

75. A dispensing assembly as claimed in claim 51, in which the dispenser body comprises:-

an inner part having a system liquid portion forming some of the main bore;

a nozzle mounting part having a sample liquid portion forming the remainder of the main bore;

a divider barrier comprising at least three closely contacting members at least one member being secured to each of the parts.

76. A dispensing assembly as claimed in claim 8, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion and the divider barrier is pre-stretched.

77. A dispensing assembly as claimed in claim 8, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties and the divider barrier is pre-stretched.

78. A dispensing assembly as claimed in claim 15, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate

sample liquid portions divided from the one system liquid portion and the divider barrier is pre-stretched.

79. A dispensing assembly as claimed in claim 15, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties and the divider barrier is pre-stretched.

80. A dispensing assembly as claimed in claim 21, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion and the divider barrier is pre-stretched.

81. A dispensing assembly as claimed in claim 21, in which the dispenser body mounts a plurality of nozzles and the divider barrier additionally separates portion of the main bore adjacent each nozzle entrance to form separate sample liquid portions divided from the one system liquid portion by individual divider barriers, the divider barriers forming at least two sets of divider barriers, each set having different elastomeric properties and the divider barrier is pre-stretched.

82. A dispensing assembly as claimed in any preceding claim comprising a separate system liquid pressurising means for the rapid expulsion of sample liquid.

83. A dispensing assembly as claimed in any preceding claim comprising;

an electrode incorporated in the dispensing tip;

a separate receiving electrode remote from the tip; and

a high voltage source connected to one of the electrodes to provide an electrostatic field therebetween.

84. A dispensing assembly as claimed in claim 83 in which the receiving electrode is below the dispensing tip.

85. A dispensing assembly as claimed in claim 83 or 84 in which a droplet receiving substrate is mounted between the receiving electrode and the dispenser tip.

86. A dispensing assembly as claimed in claim 83 or 84 in which a droplet receiving substrate is mounted below the receiving electrode, the receiving electrode having at least one hole for the droplet to pass through to the receiving substrate.

87. A dispensing assembly as claimed in claim 85 or 86 in which there is a plurality of receiving electrodes at least one of which is activated at any time.

88. A dispensing assembly as claimed in any of claims 83 to 87 in which synchronous indexing means are provided for the dispenser and the receiving electrode for accurate deployment of droplets on the substrate.

89. A dispensing assembly as claimed in any of claims 83 to 88 in which there is more than one receiving electrode forming droplet deflection electrodes which are mounted below the dispensing tip and above the droplets receiving substrate and in which the high voltage source has control means to vary the voltage applied to the deflection electrodes.

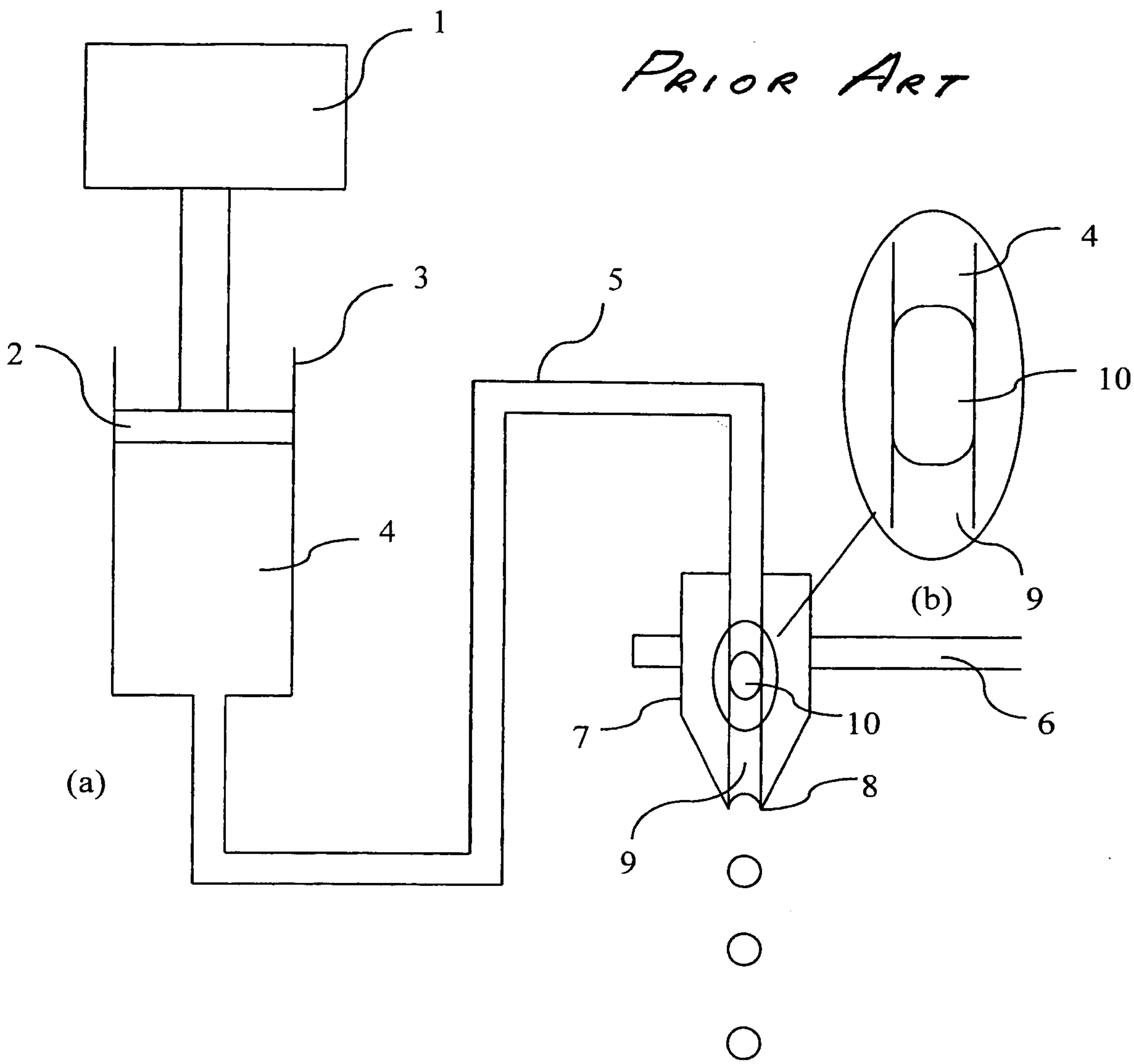

Fig. 1,

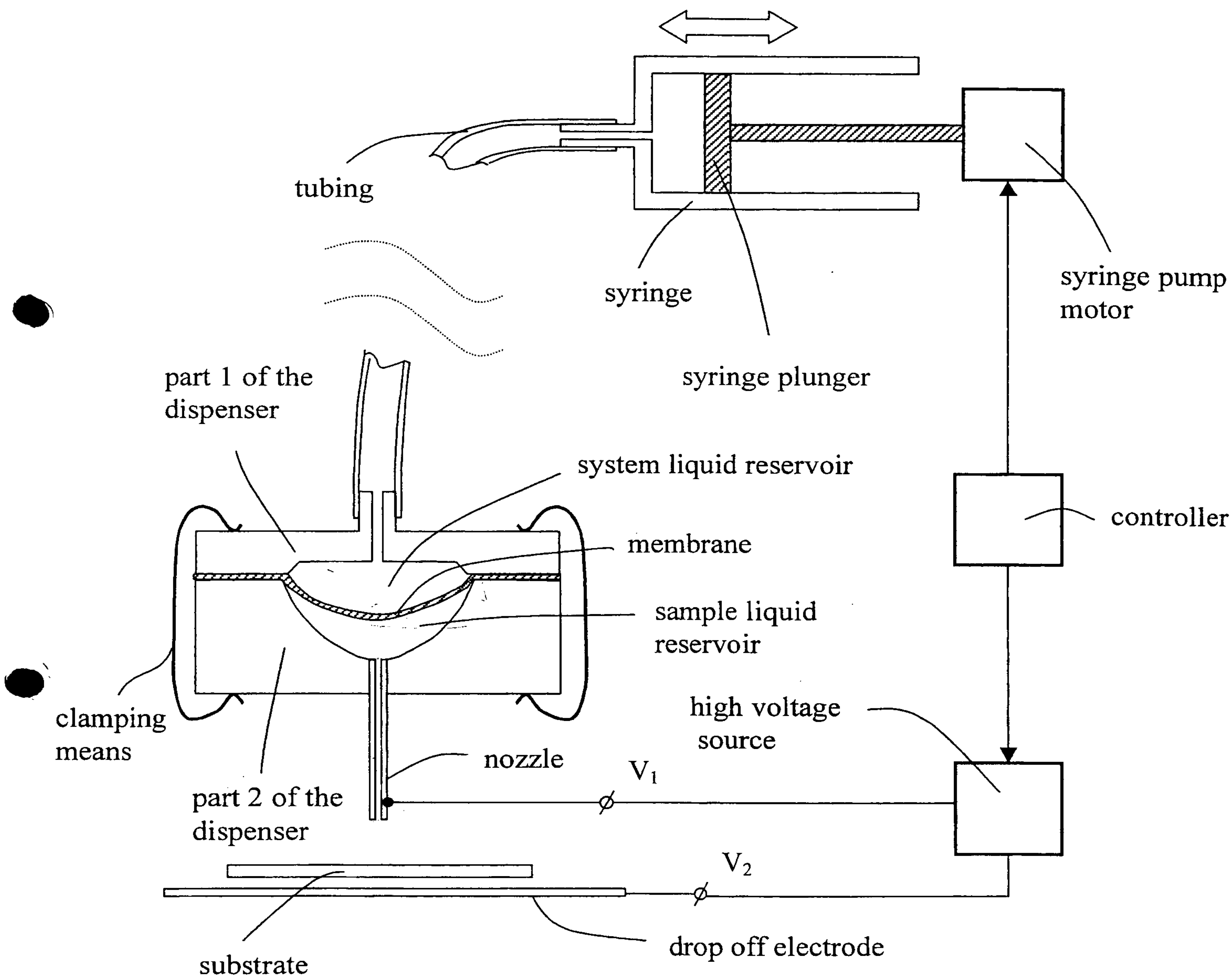

Fig. 2, [illegible] Dispensing assembly

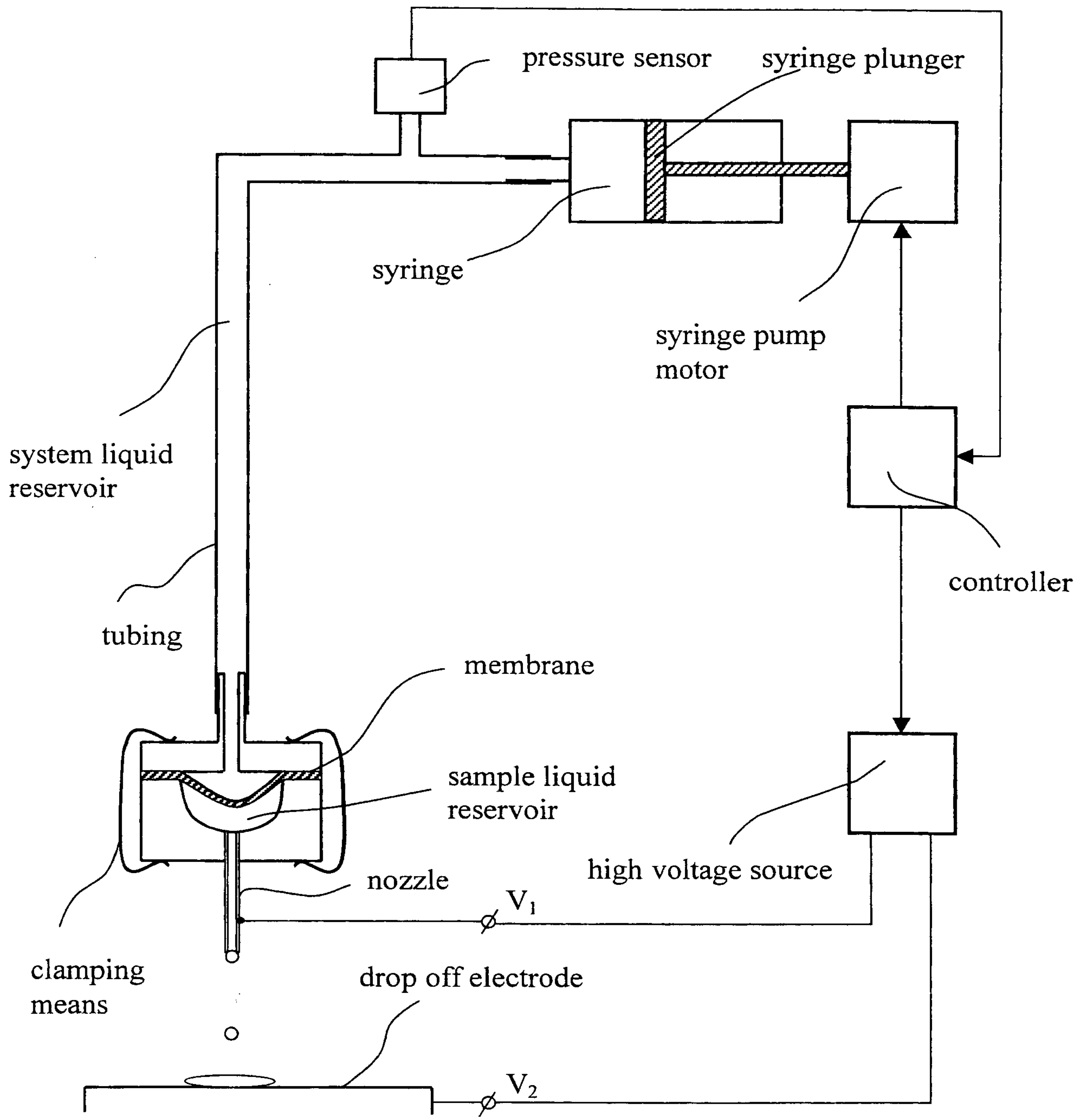

Fig. 3, Dispensing assembly with pressure sensor

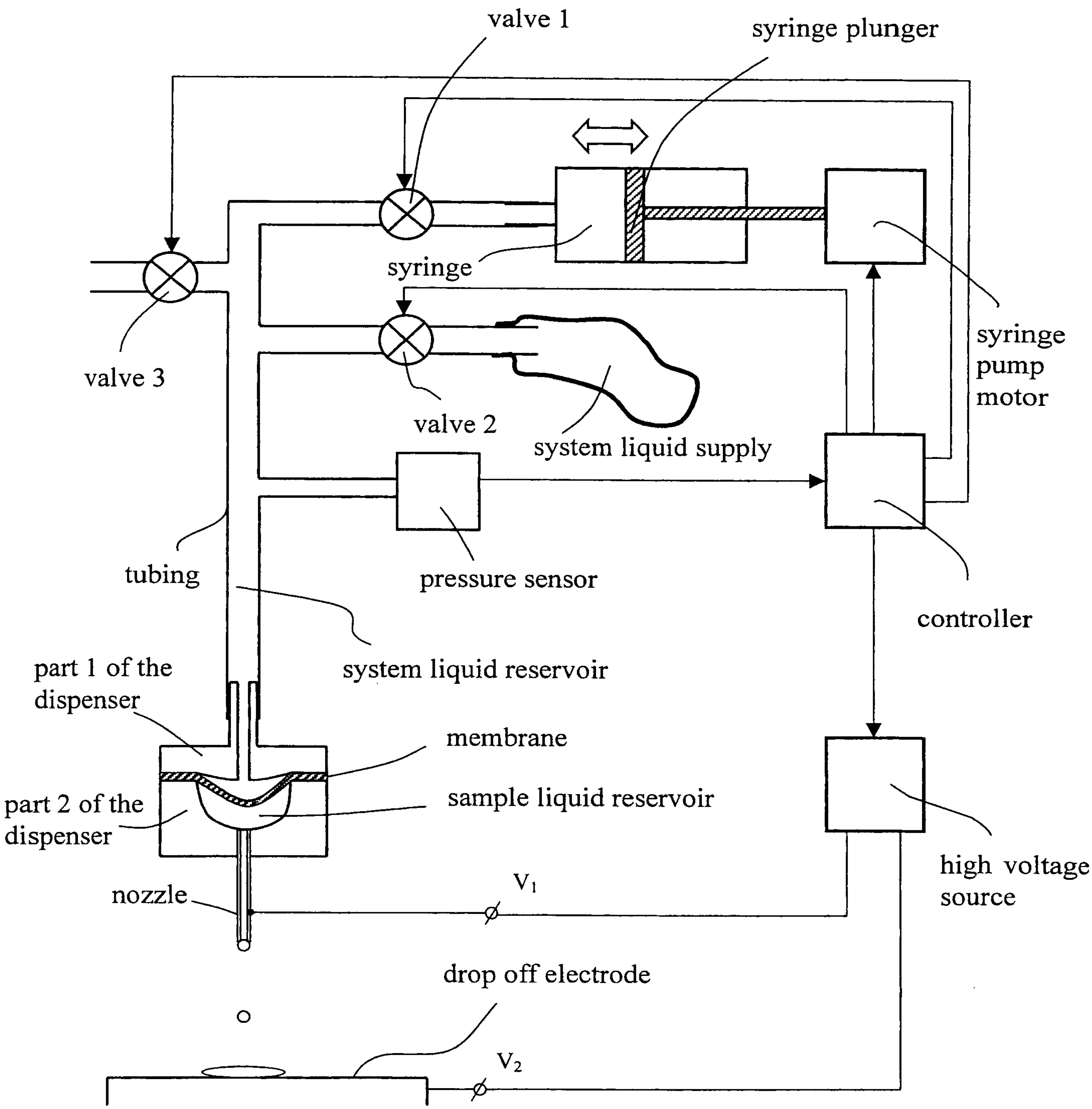

Fig. 4, Dispensing assembly with system liquid supply reservoir

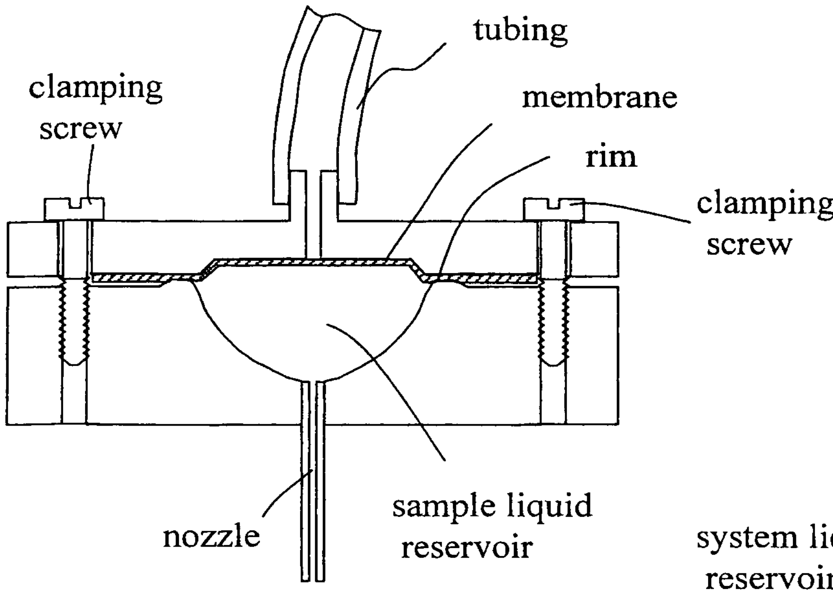

Fig. 5

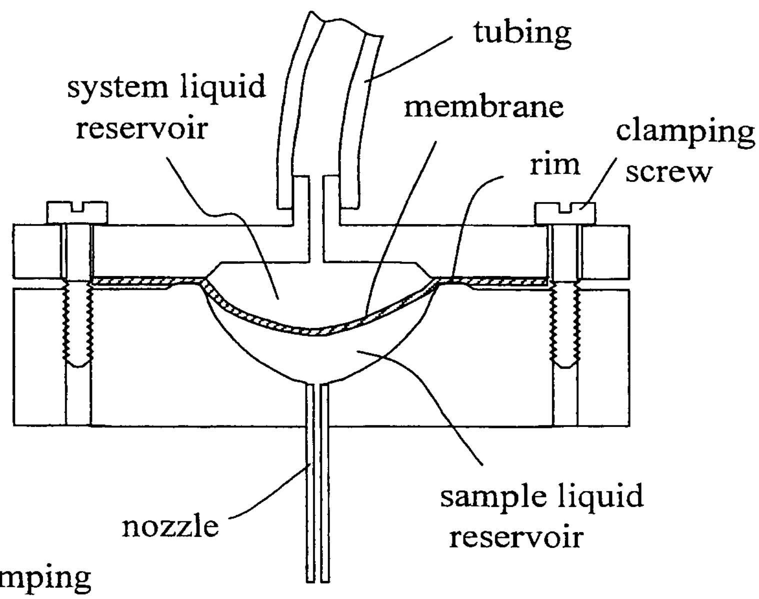

Fig. 6

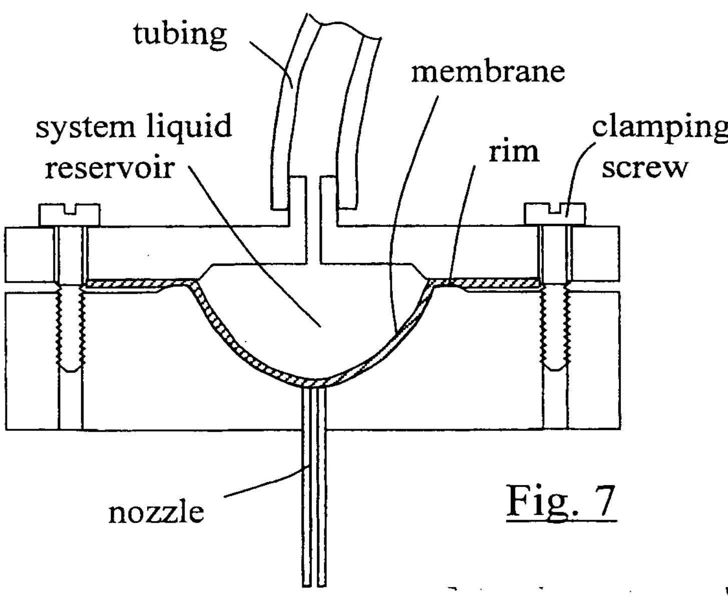

Fig. 7

Dispenser with membrane at three different positions of the membrane

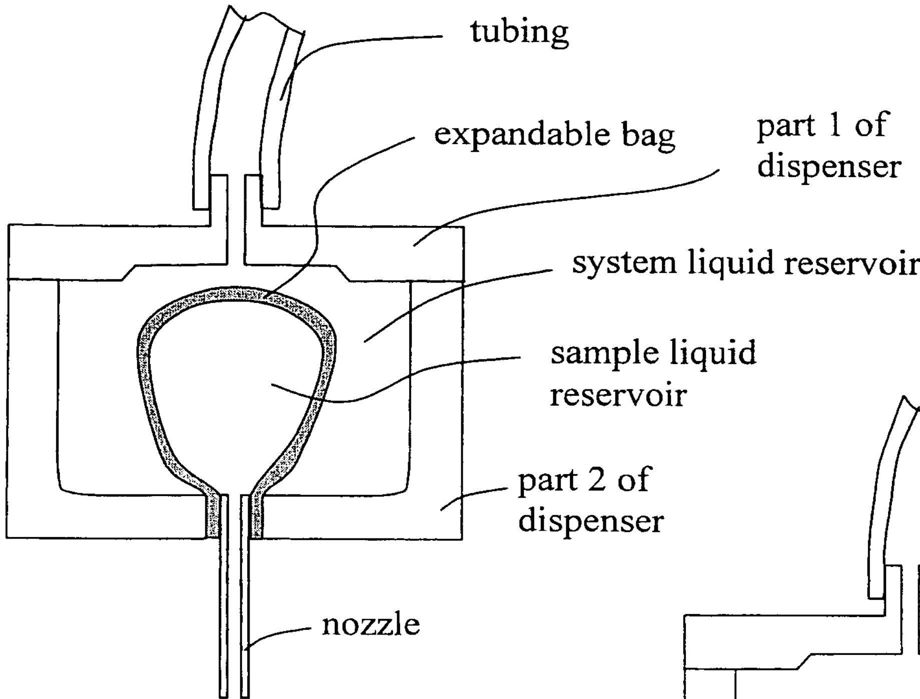

Fig. 8

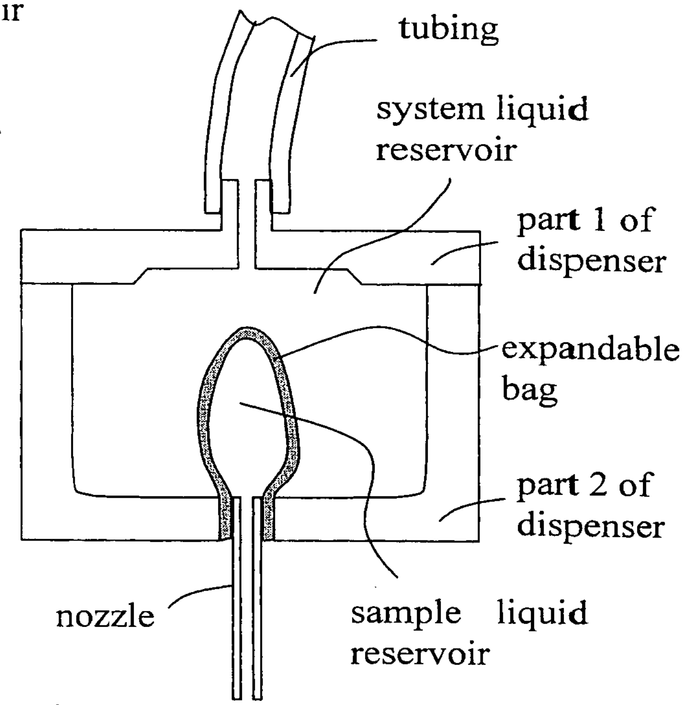

Fig. 9

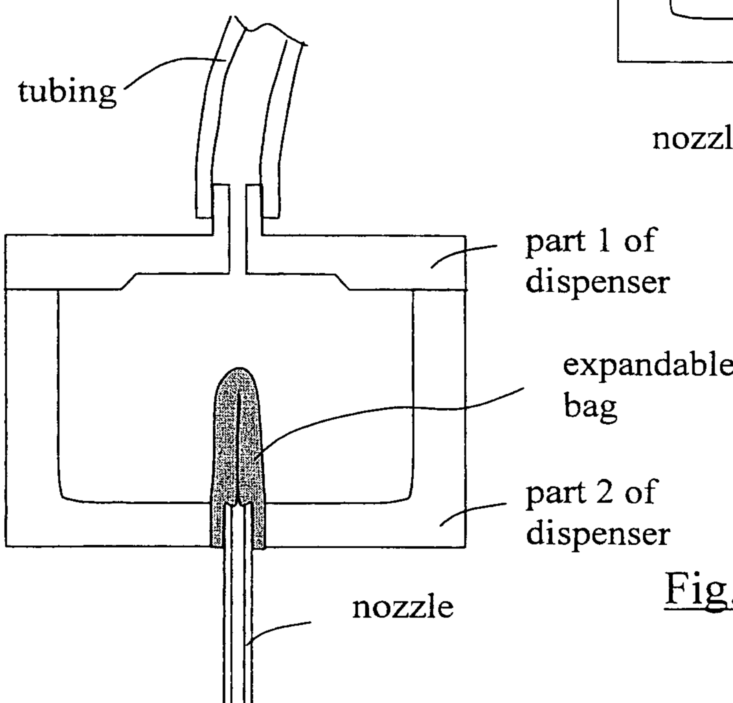

Fig. 10

Dispenser with expandable bag

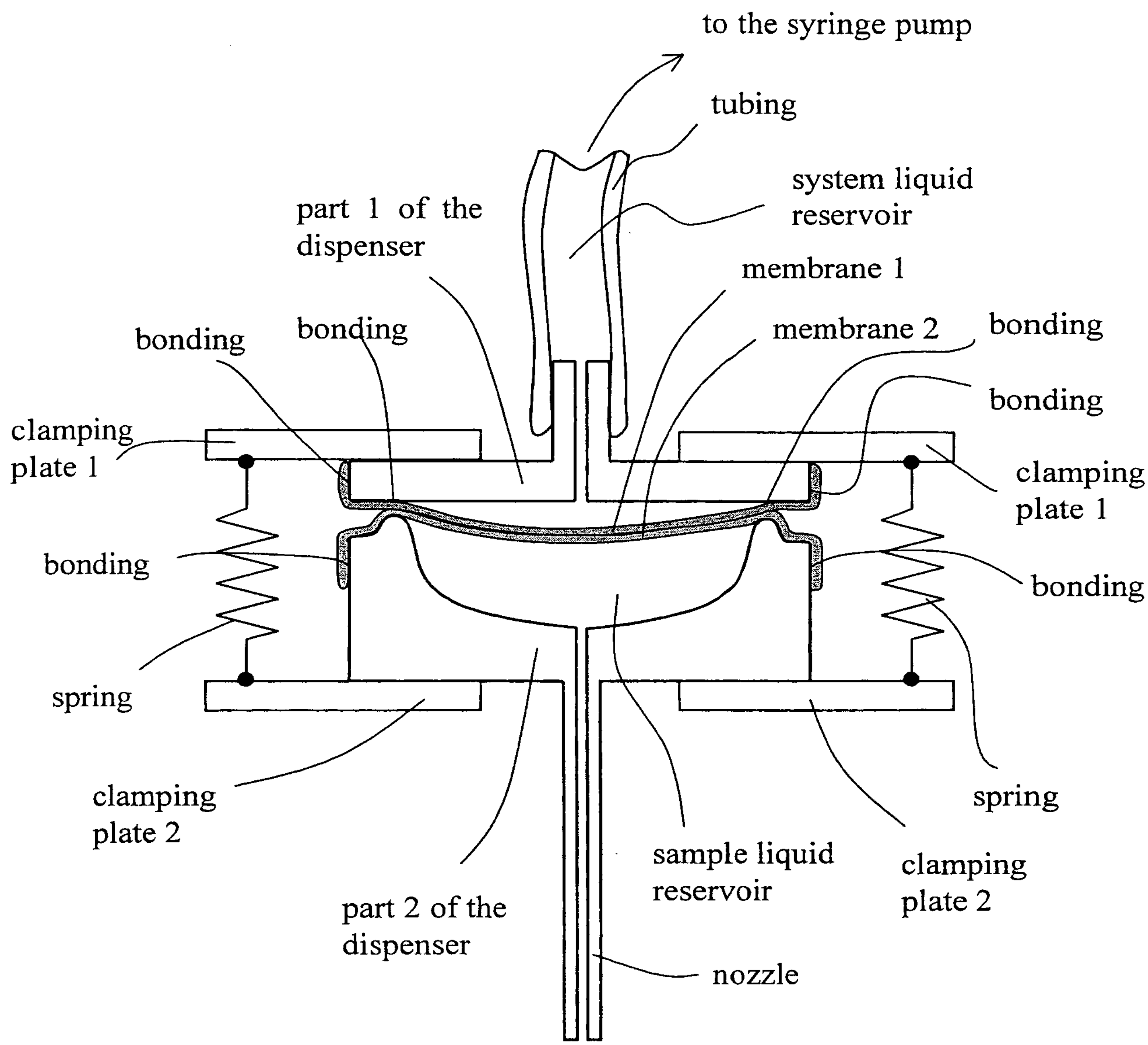

Fig. 11, Dispenser with disposable part 2.

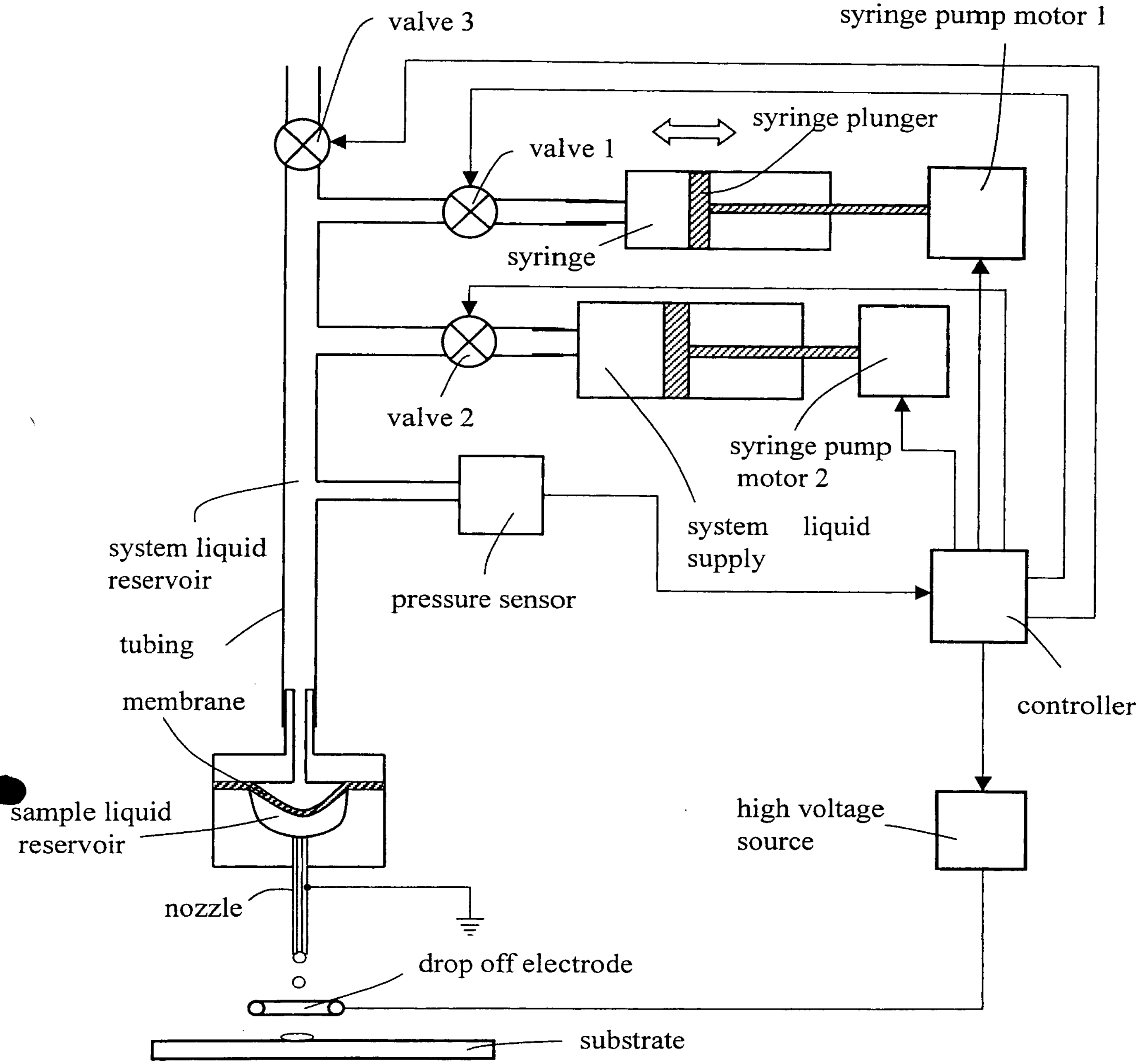

Fig. 12, [illegible] . Dispensing assembly with one drop off electrode.

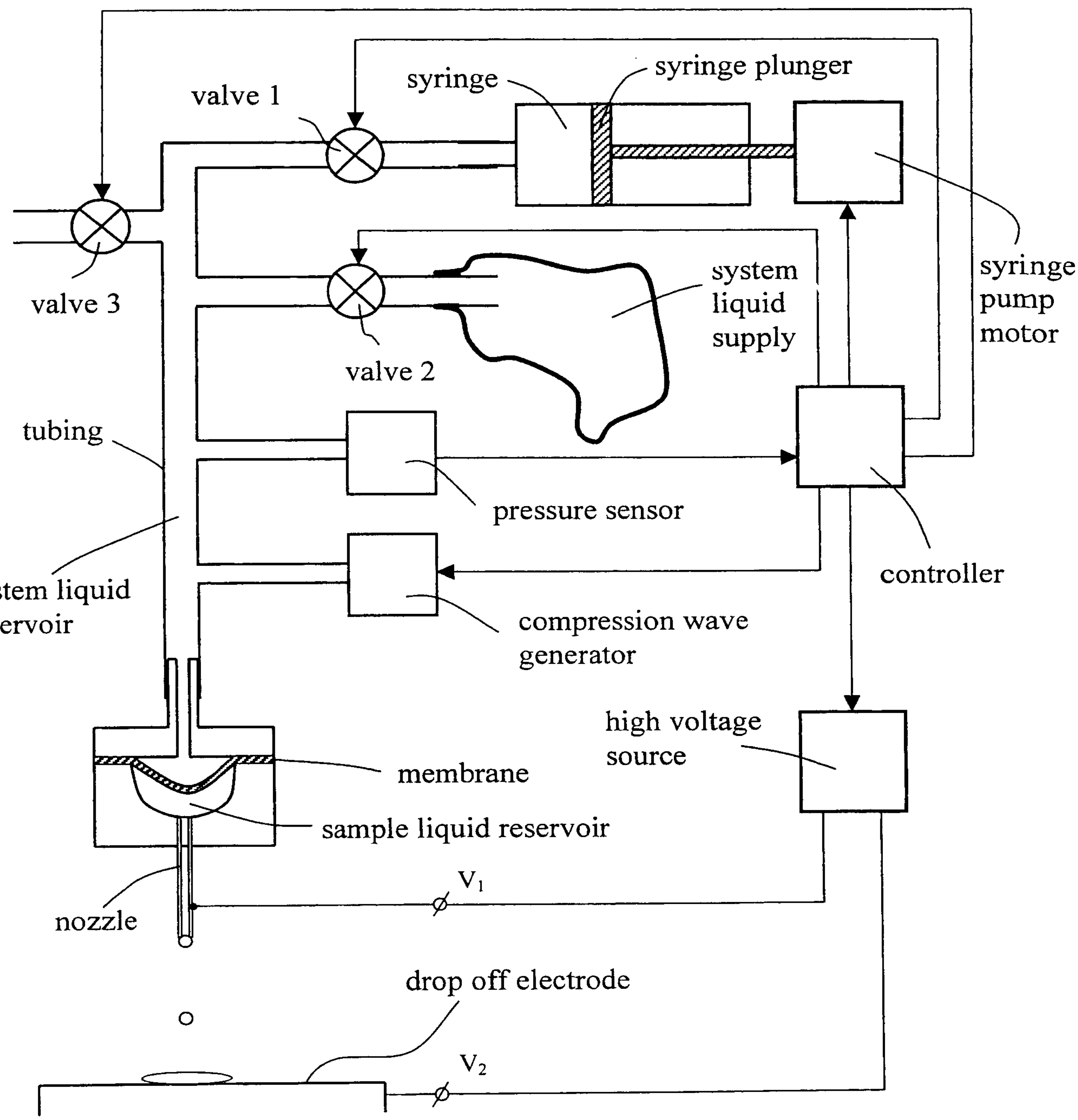

Fig. 13, Dispensing assembly with a compression

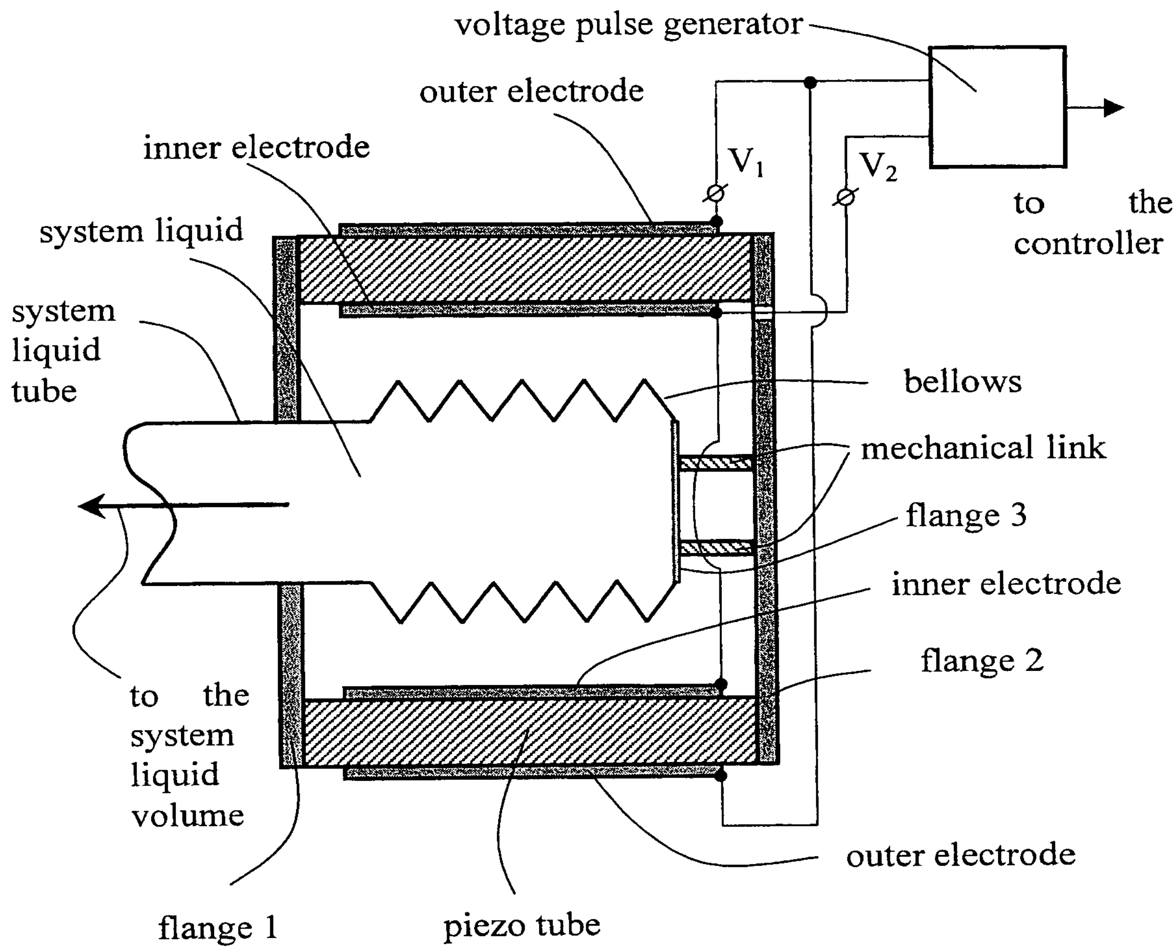

Fig. 14, Compession wave generator using a piezoactuator.

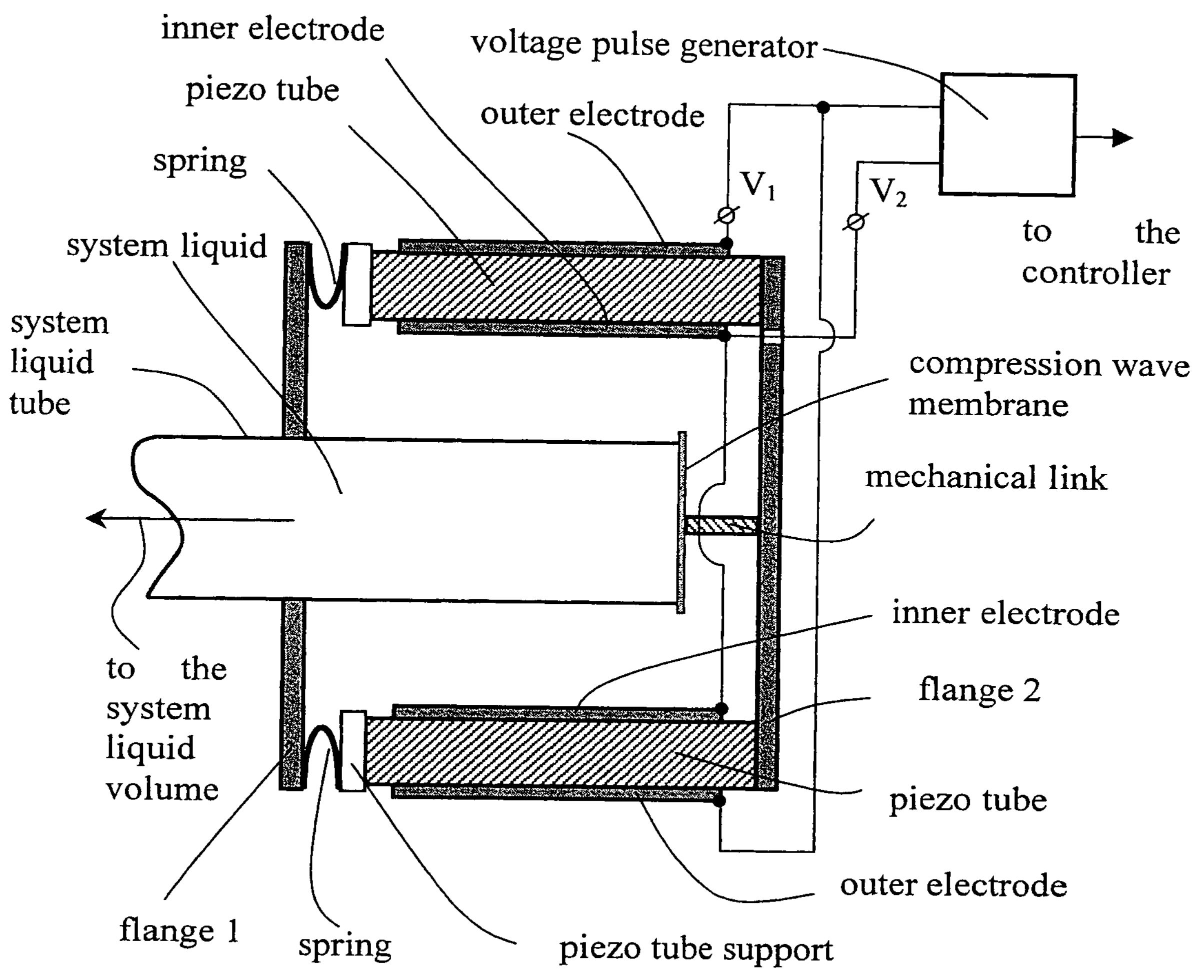

Fig. 15, Compression wave generator using a piezoactuator.

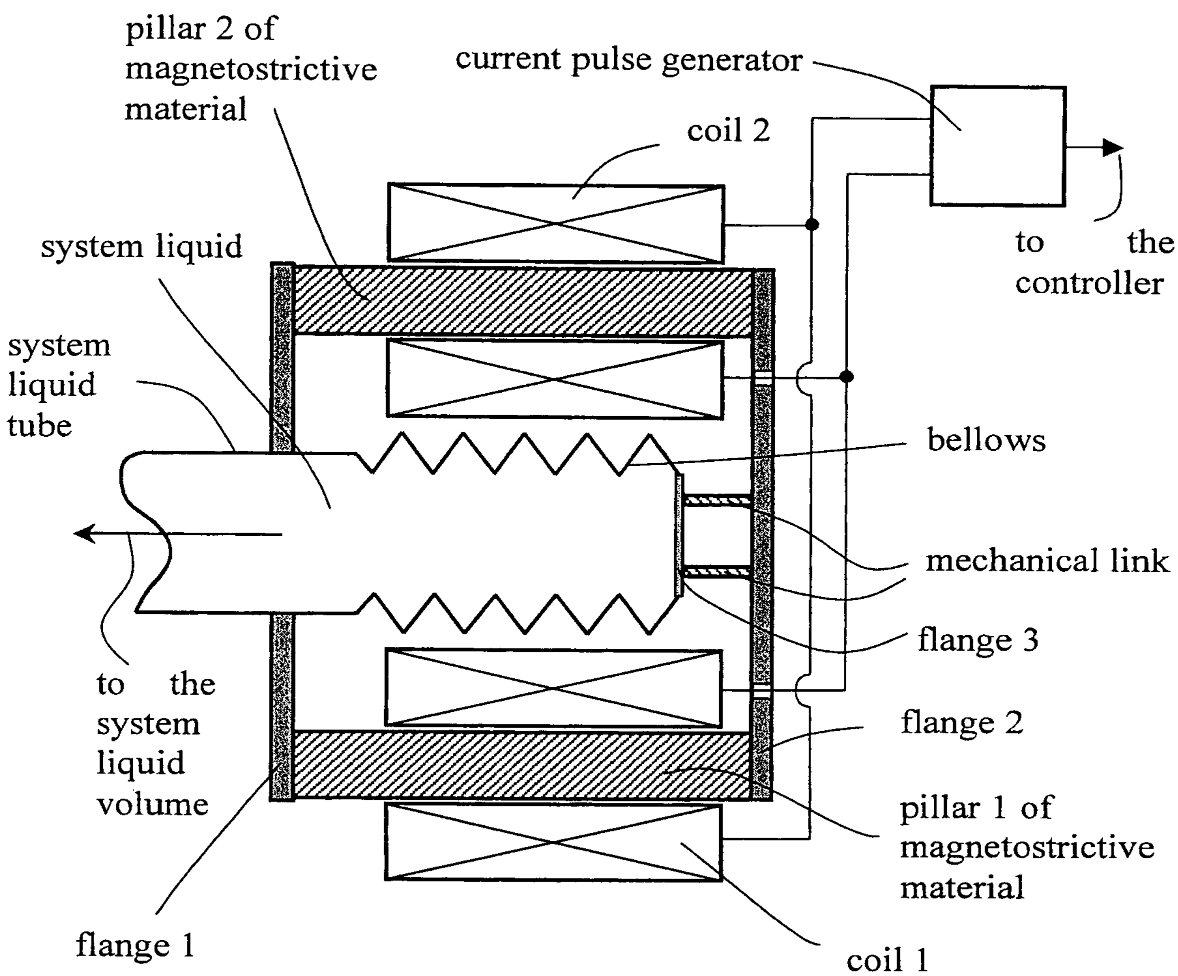

Fig. 16, . Compression wave generator using a magnetostrictive actuator.

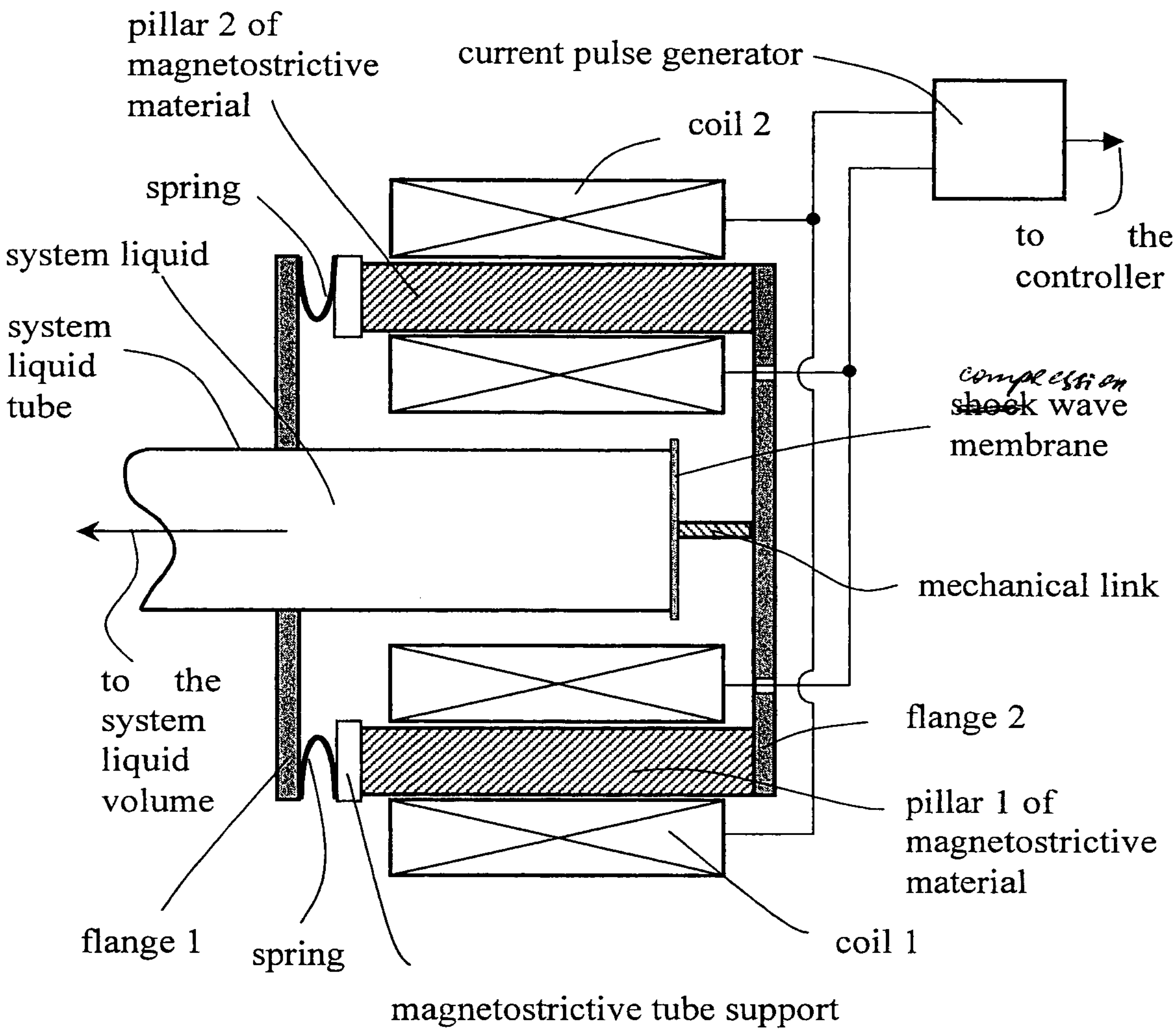

Fig. 17, Compression wave generator using a magnetostrictive actuator.

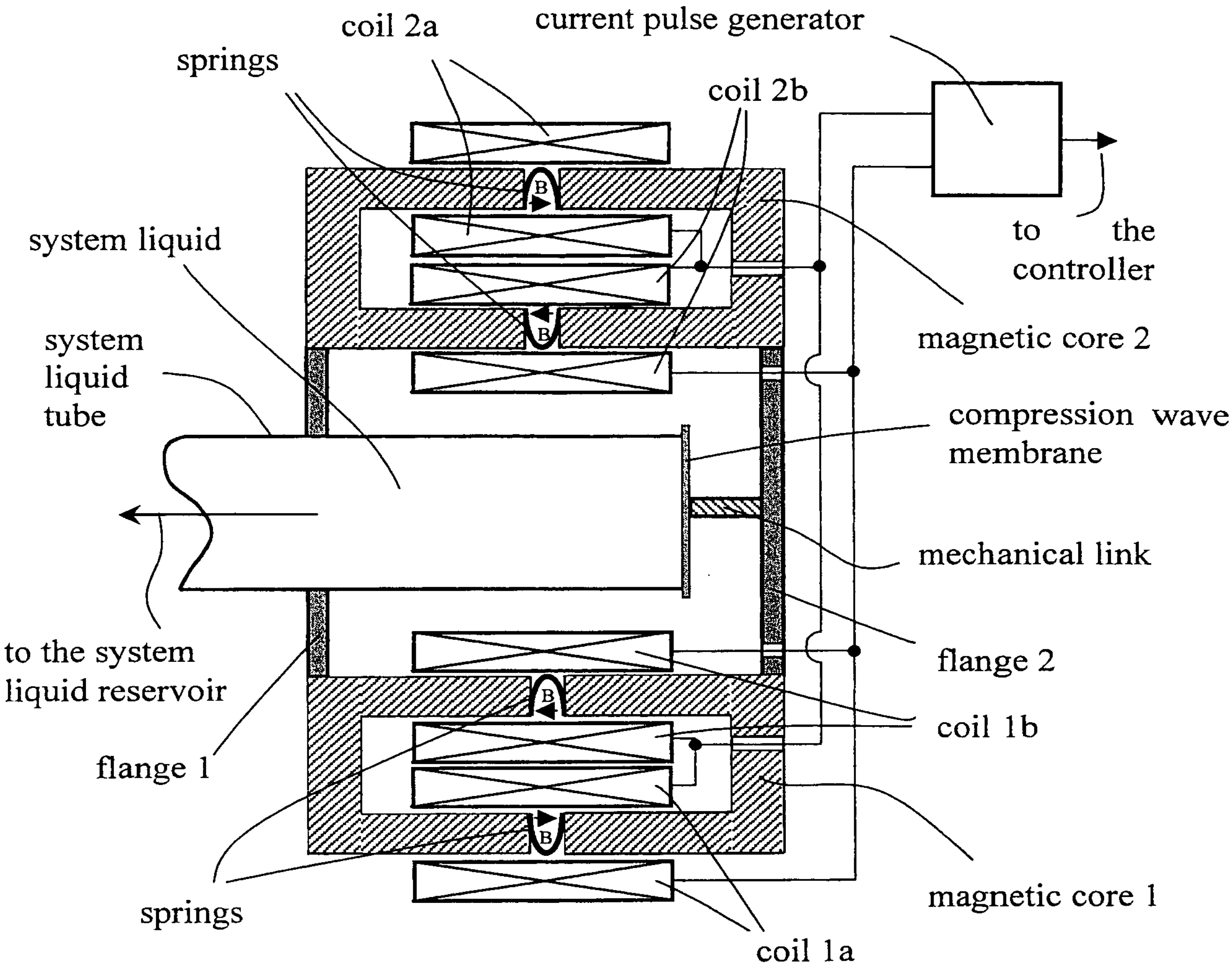

Fig. 18, Compression wave generator using a magnetic coil actuator.

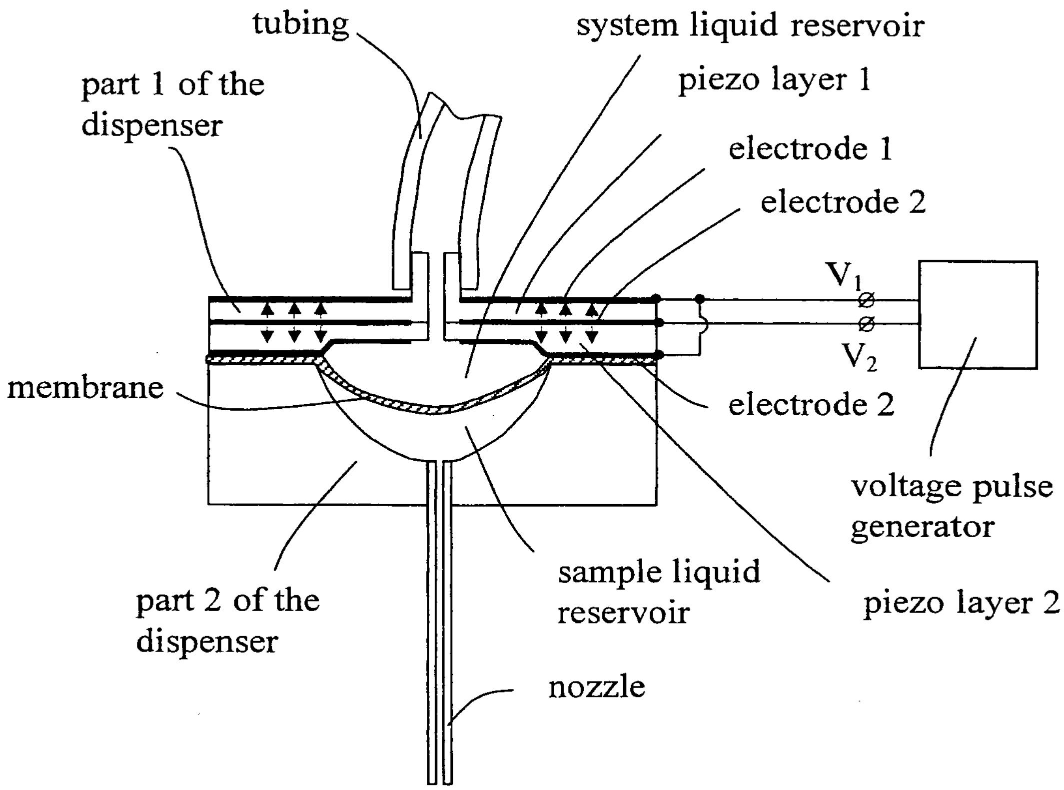

Fig.19 Compression wave generator based on piezo attached directly to the dispenser

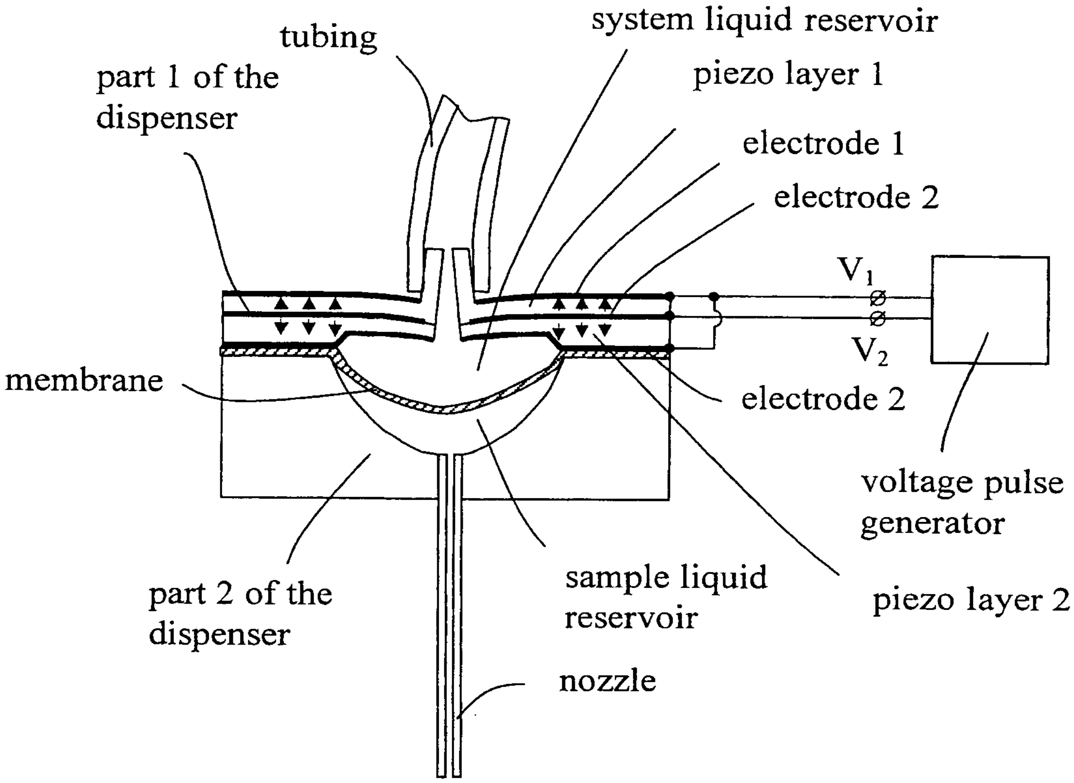

Fig.20 Compression wave generator based on piezo attached directly to the dispenser

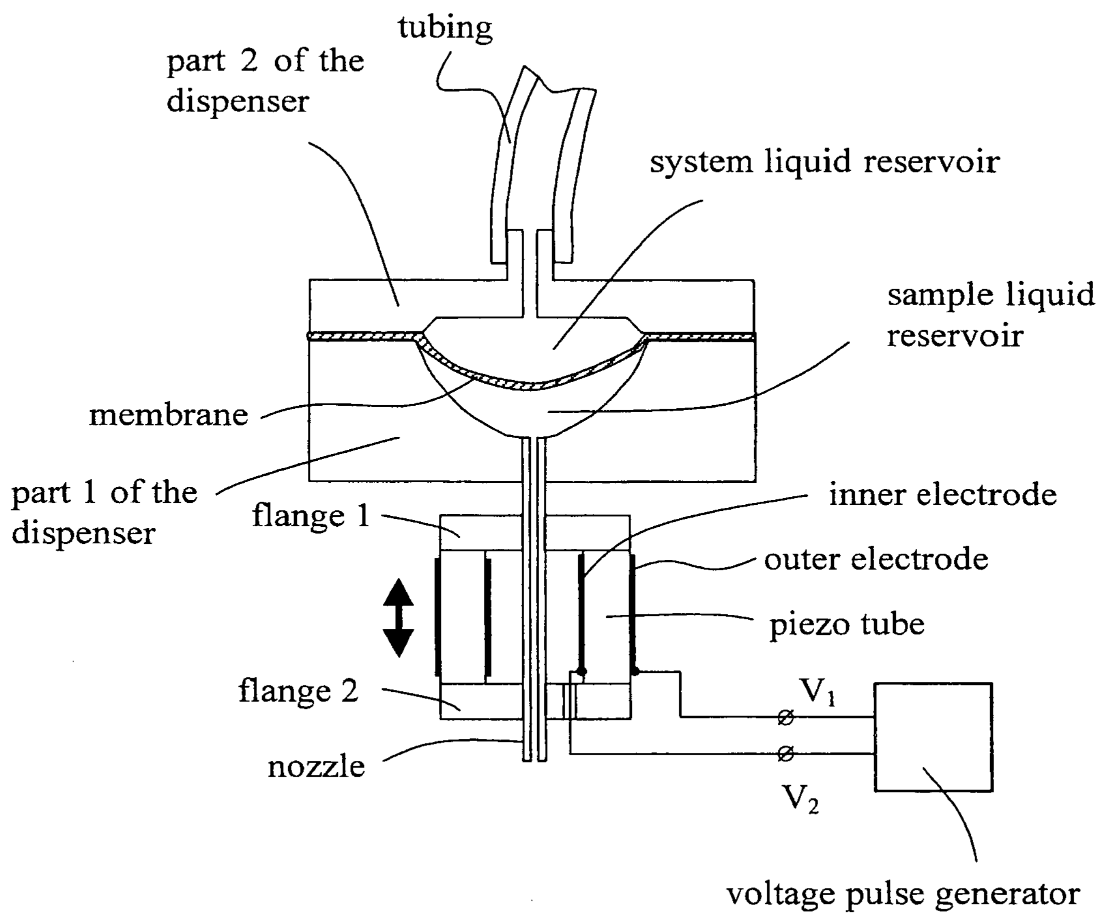

Fig. 21, Piezo actuator

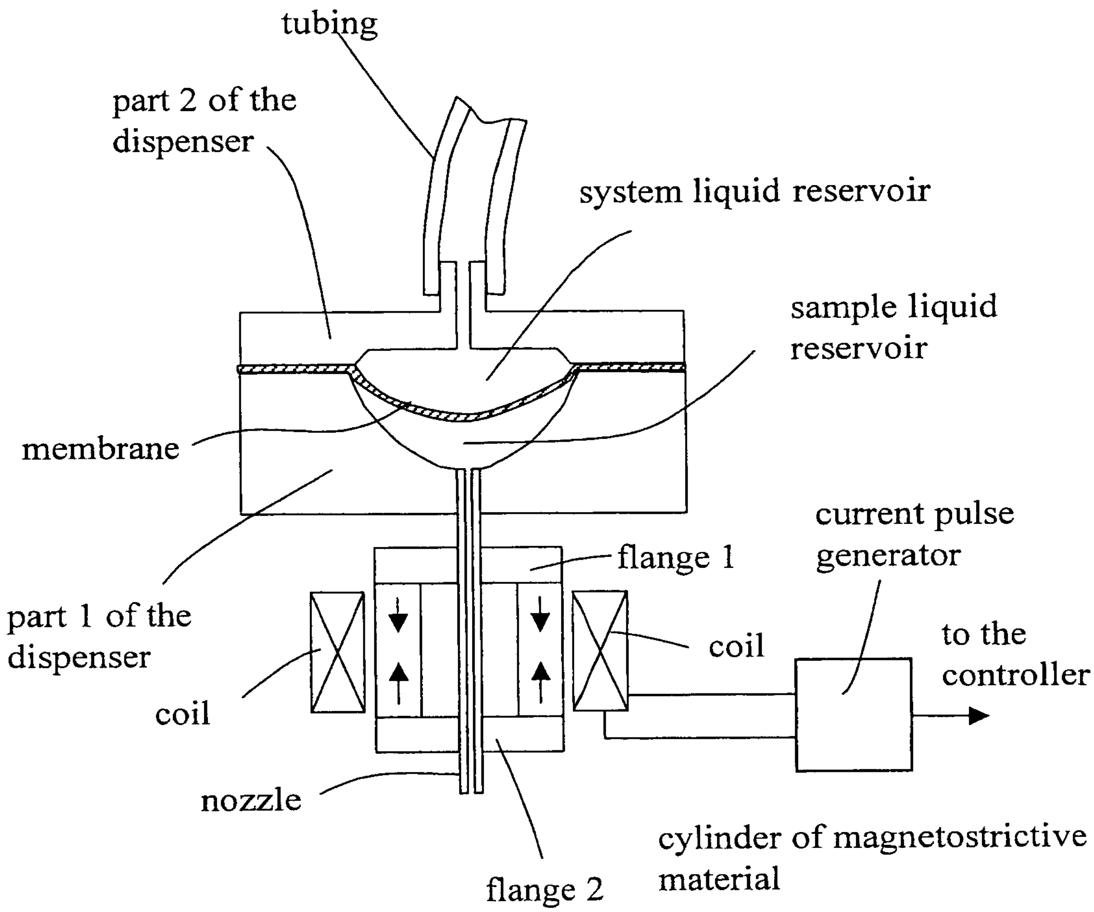

Fig. 22. Magnetostrictive actuator

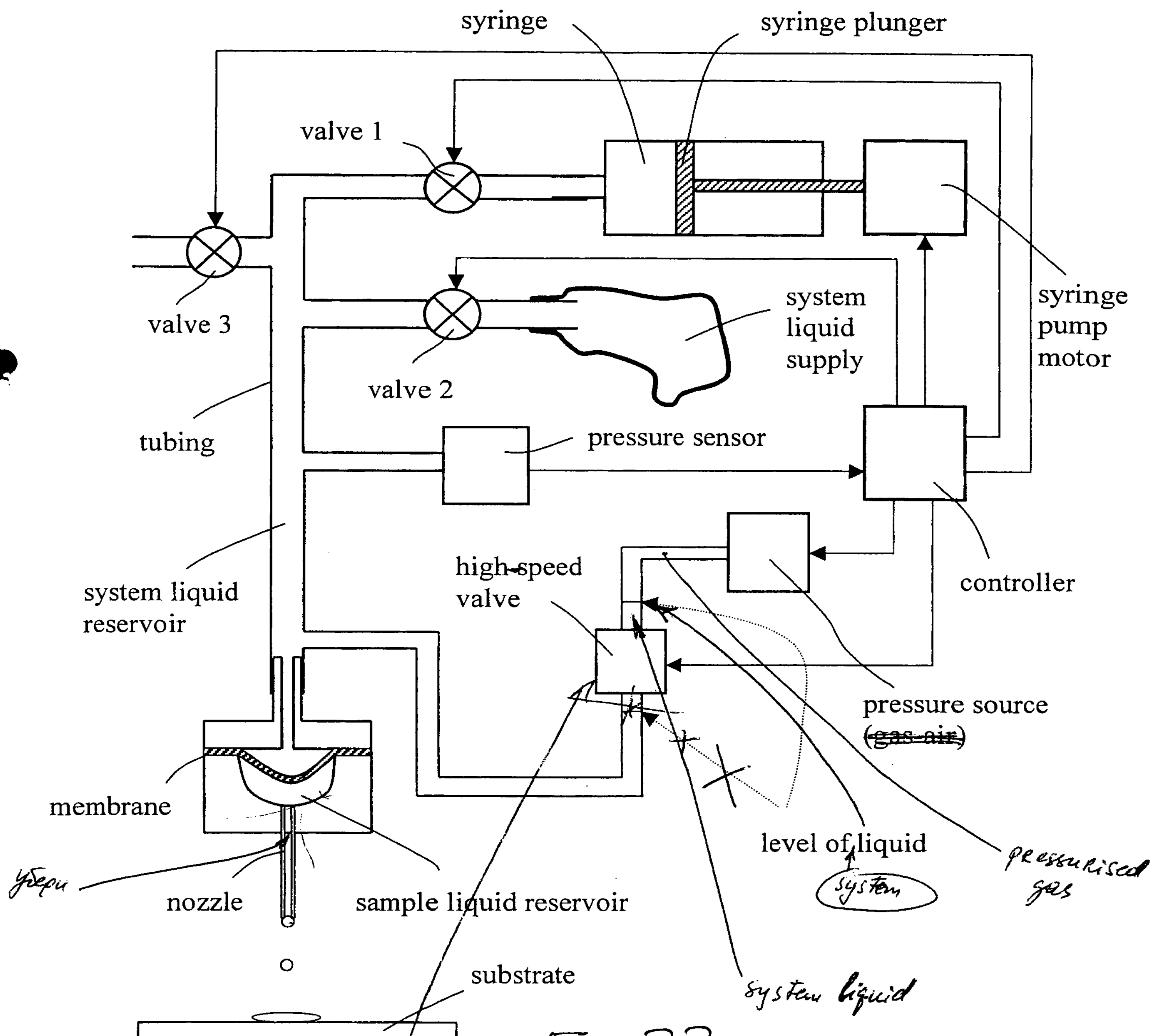

Fig 23a

Fig. 23a, Dispensing assembly with a pressure source and a high-speed valve.

Саша,
Передвинь high-speed valve пониже на рисунке, чтобы можно было нарисовать

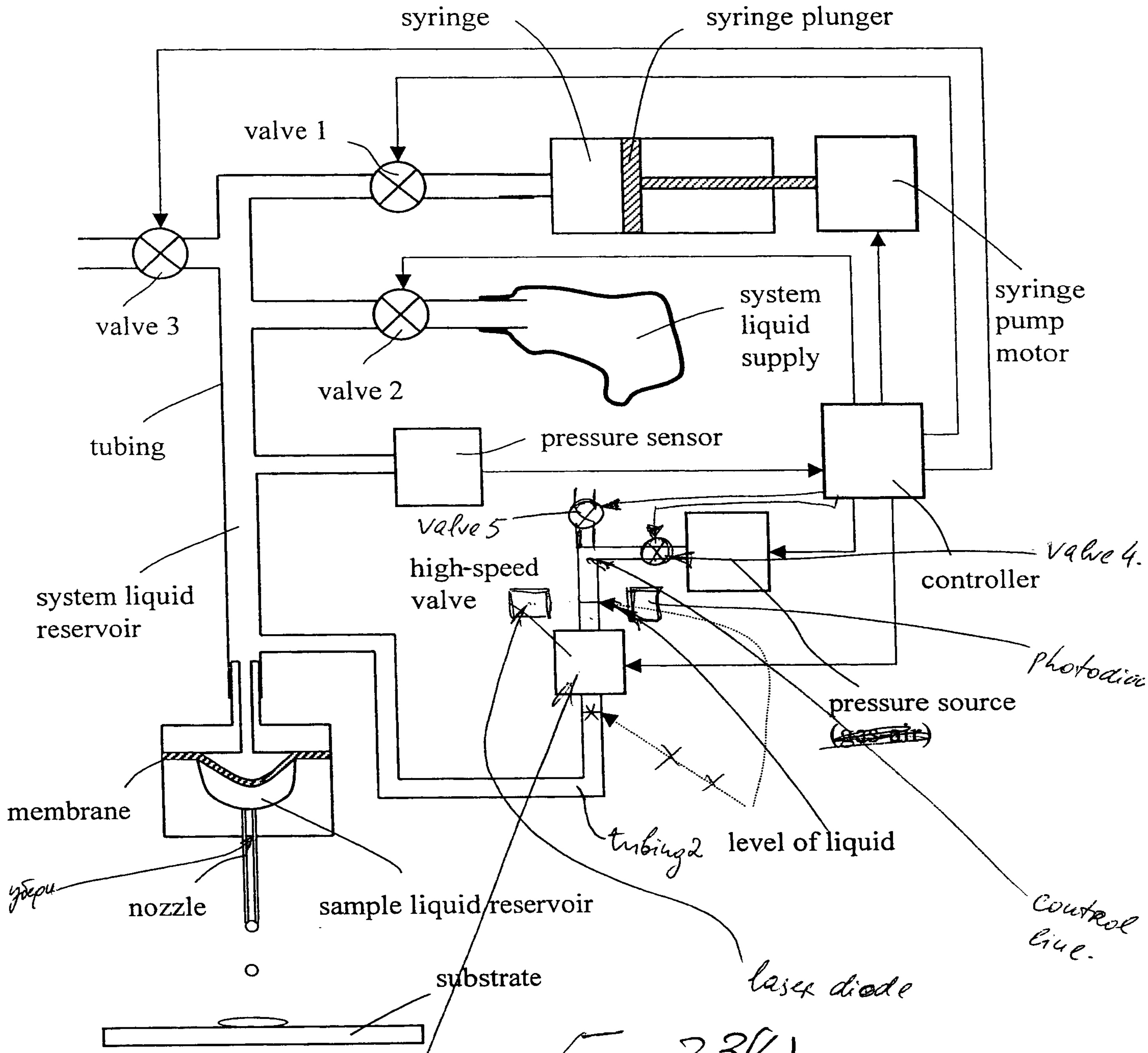

Fig 23(b)

Fig. 23, ~~Fig. 6~~ b. Dispensing assembly with a pressure wave generator with a valve.

Саша,
Передвинь ножите на рисунке.

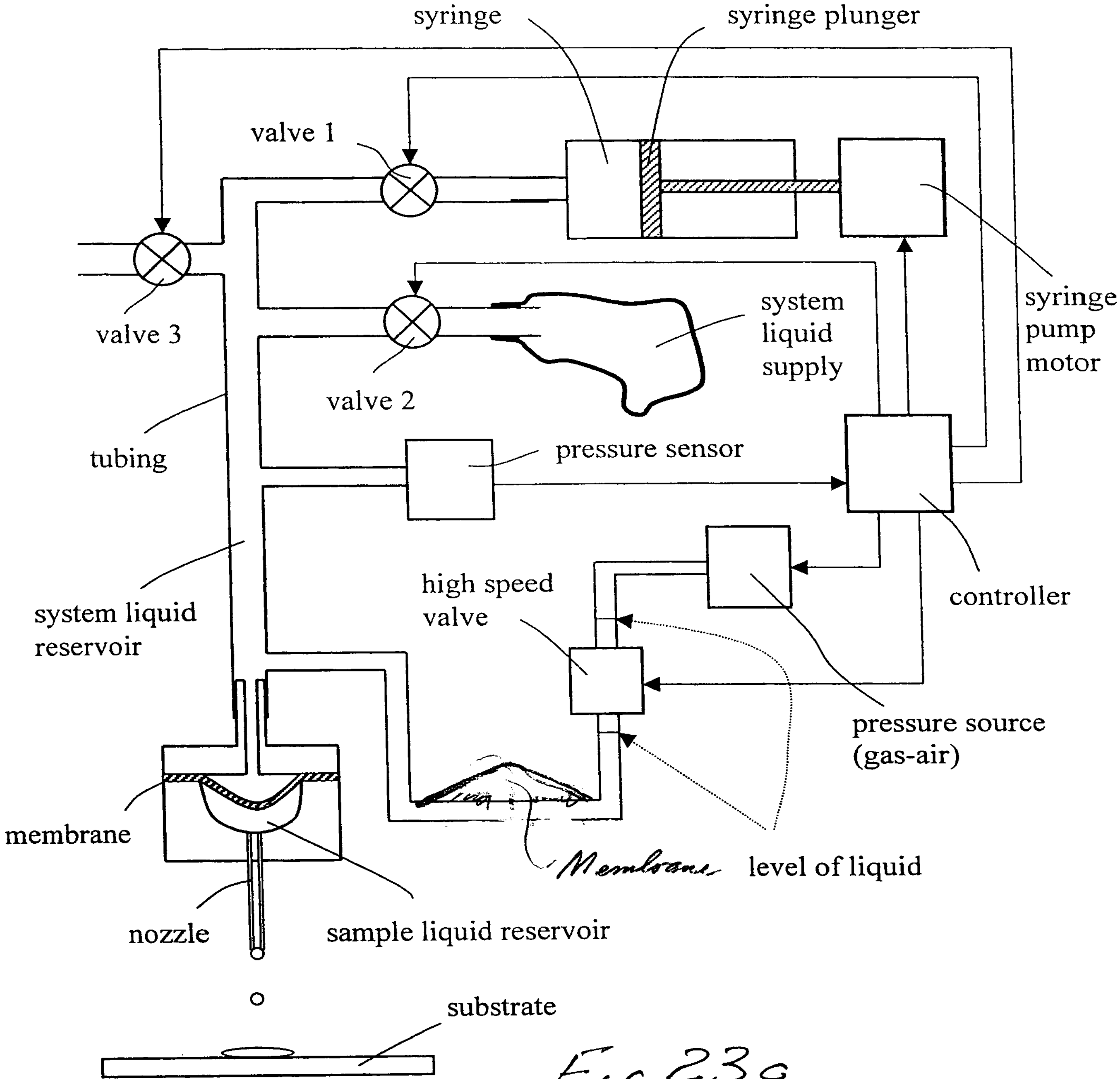

Fig 23c

Fig. 23c. Dispensing assembly with a pressure wave generator with a valve.

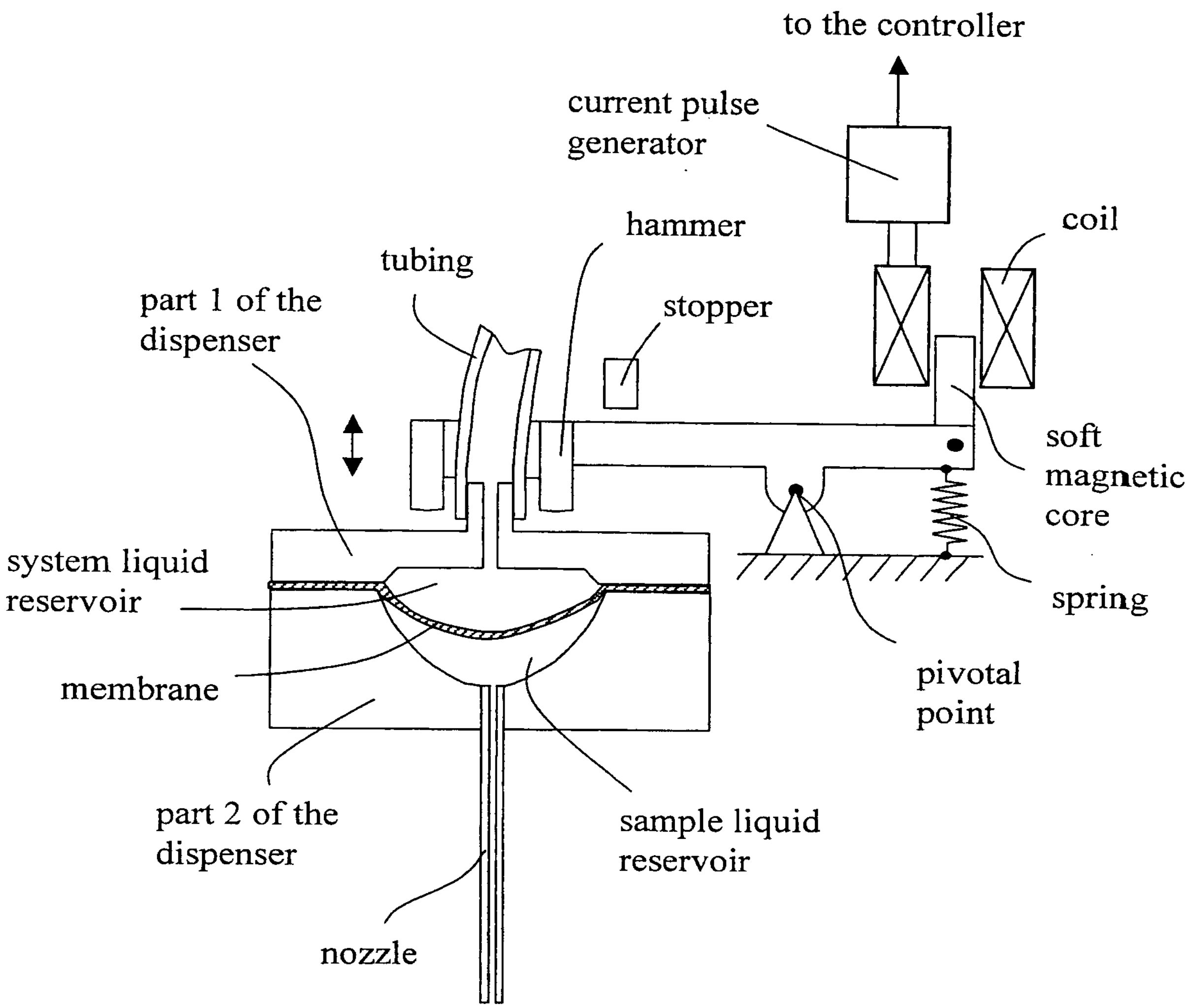

Fig. 24, [illegible]. Dispenser with magnetic coil actuator.

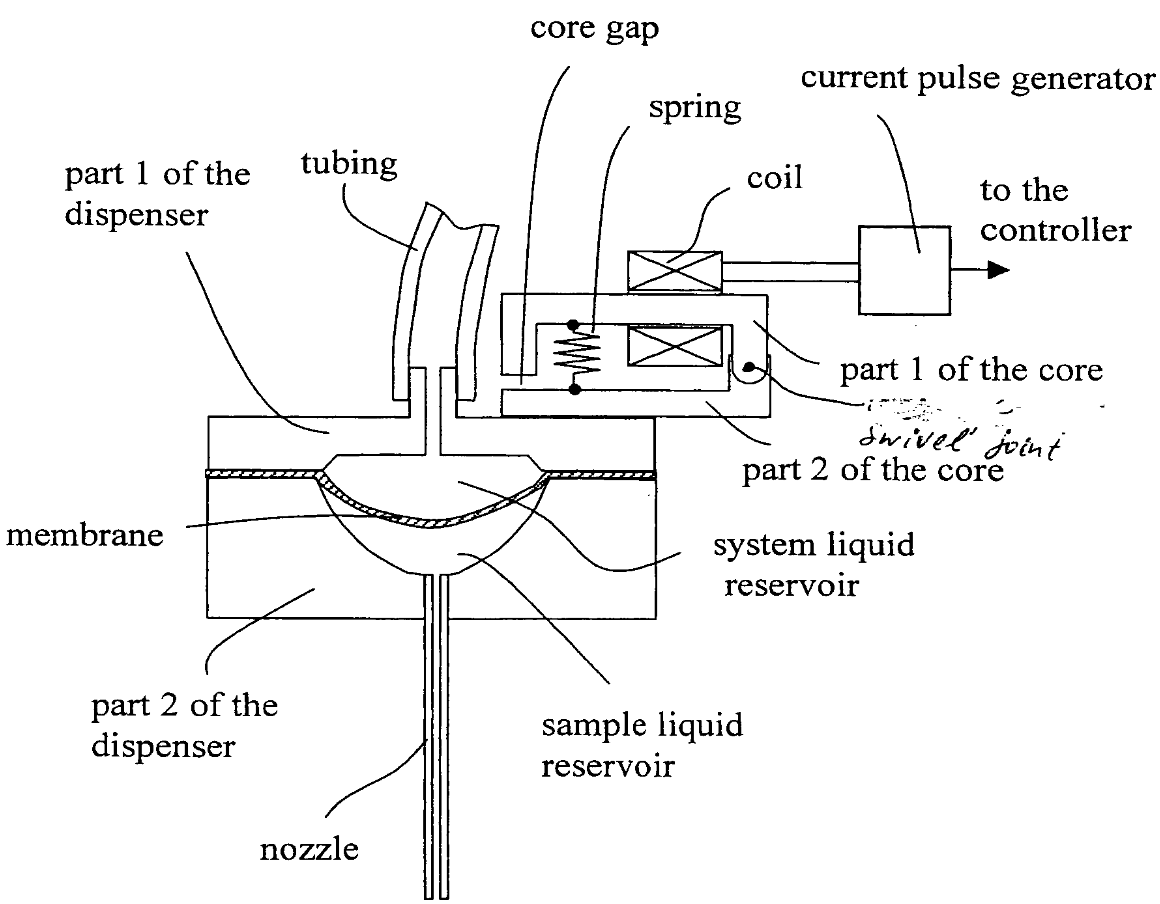

Fig. 25, Fig. 6. Dispenser with magnetic hammer heving a core of soft magnetic material

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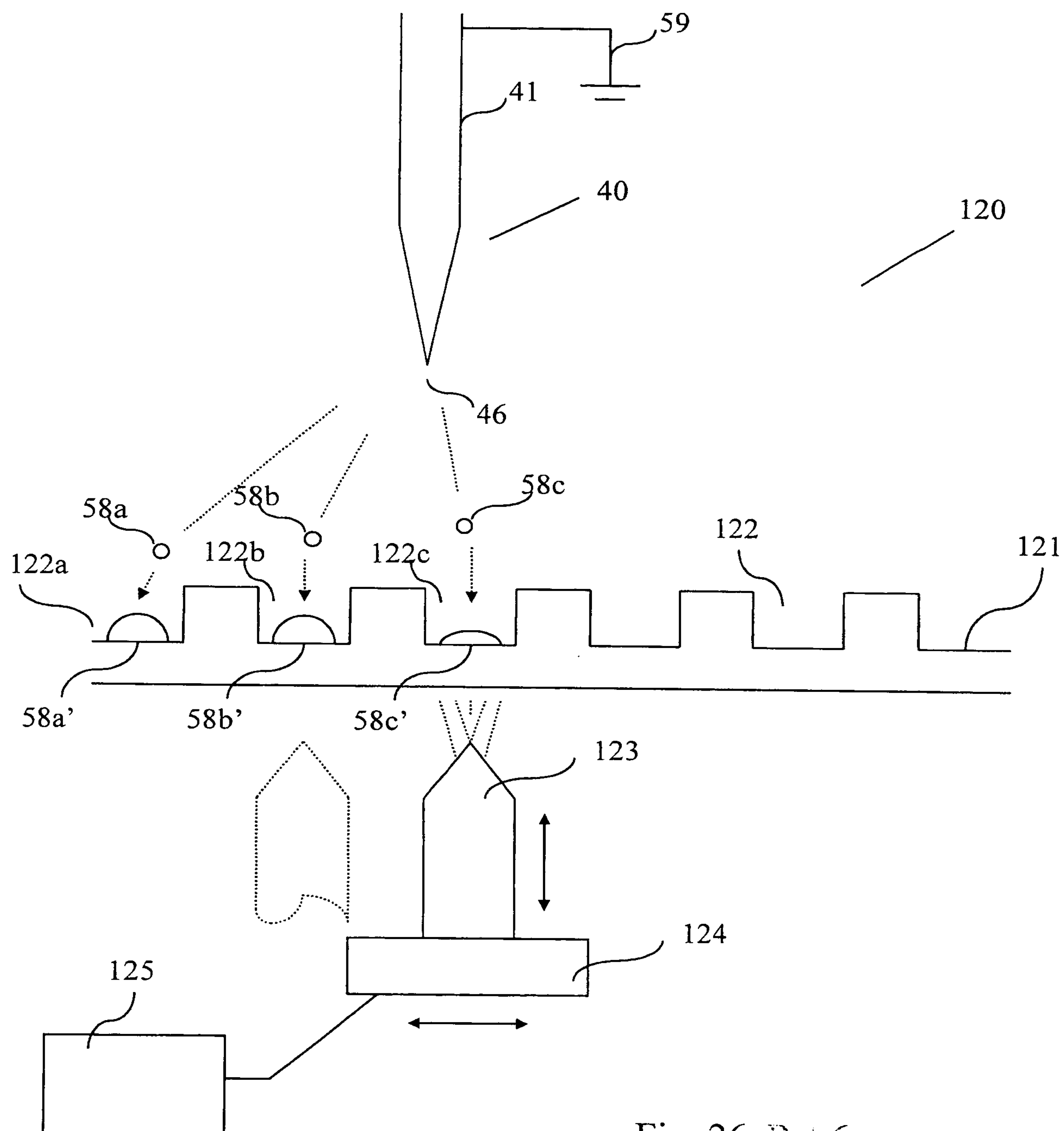

Fig. 26, Pat 6.

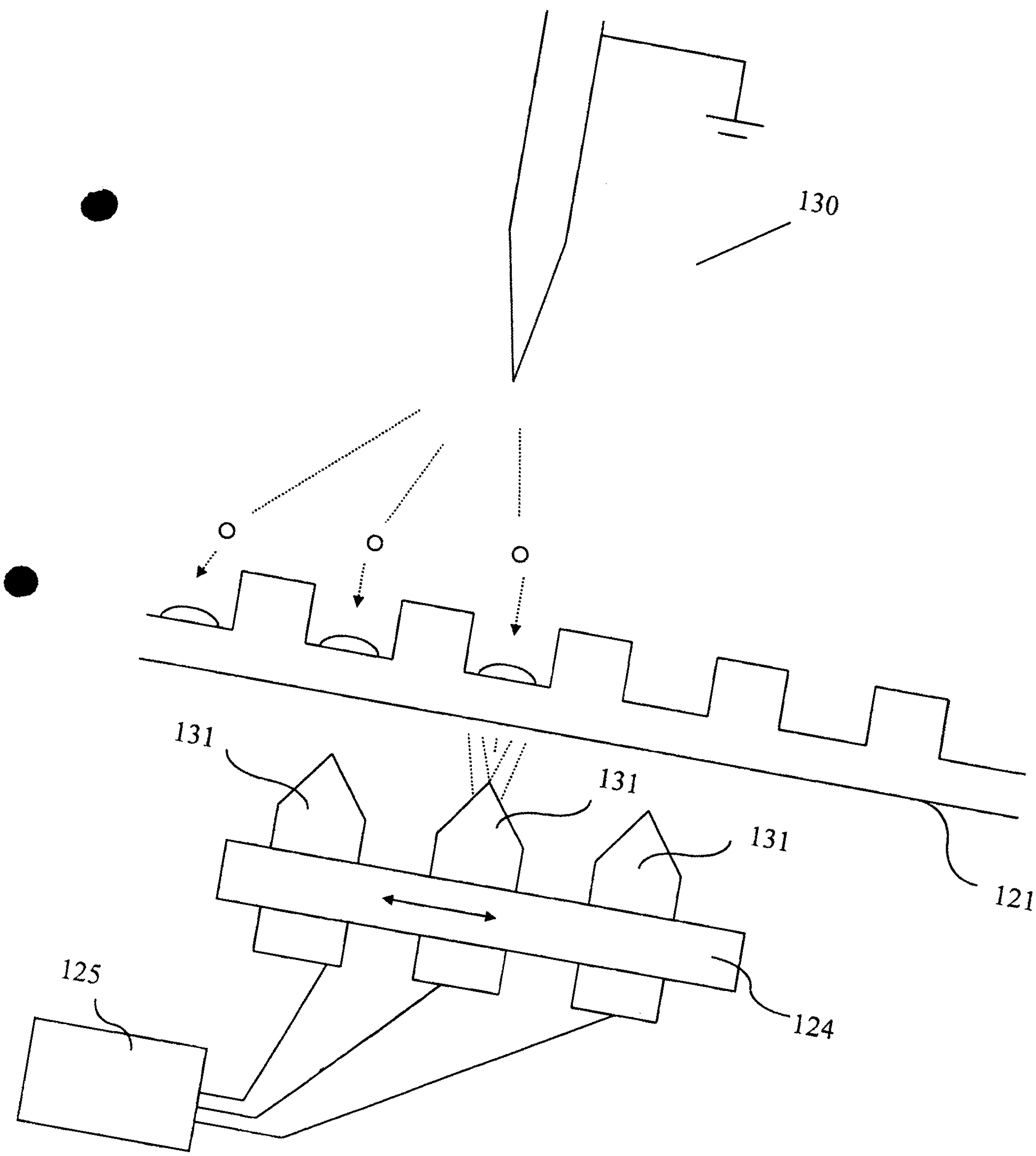

Fig. 27

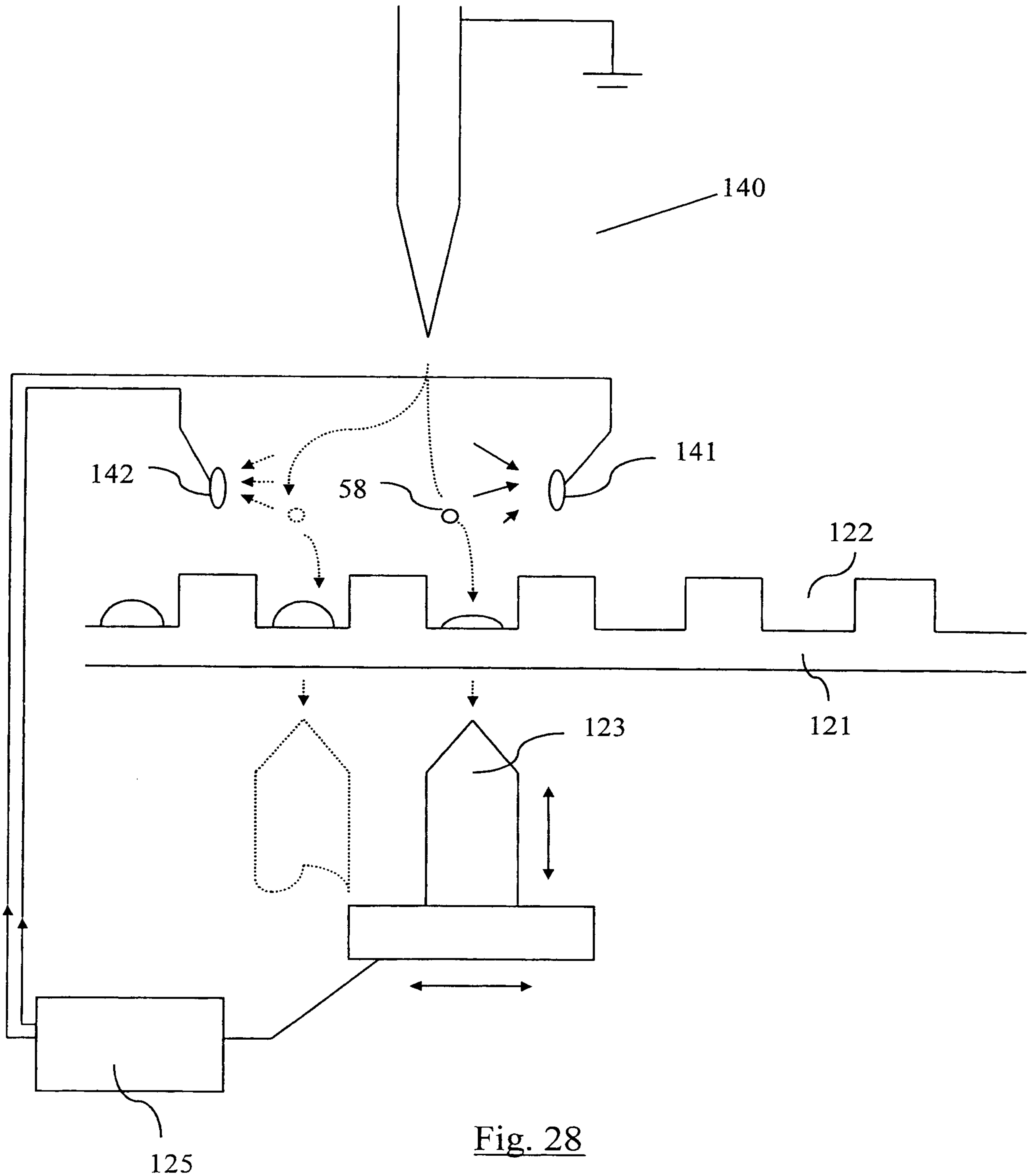

Fig. 28

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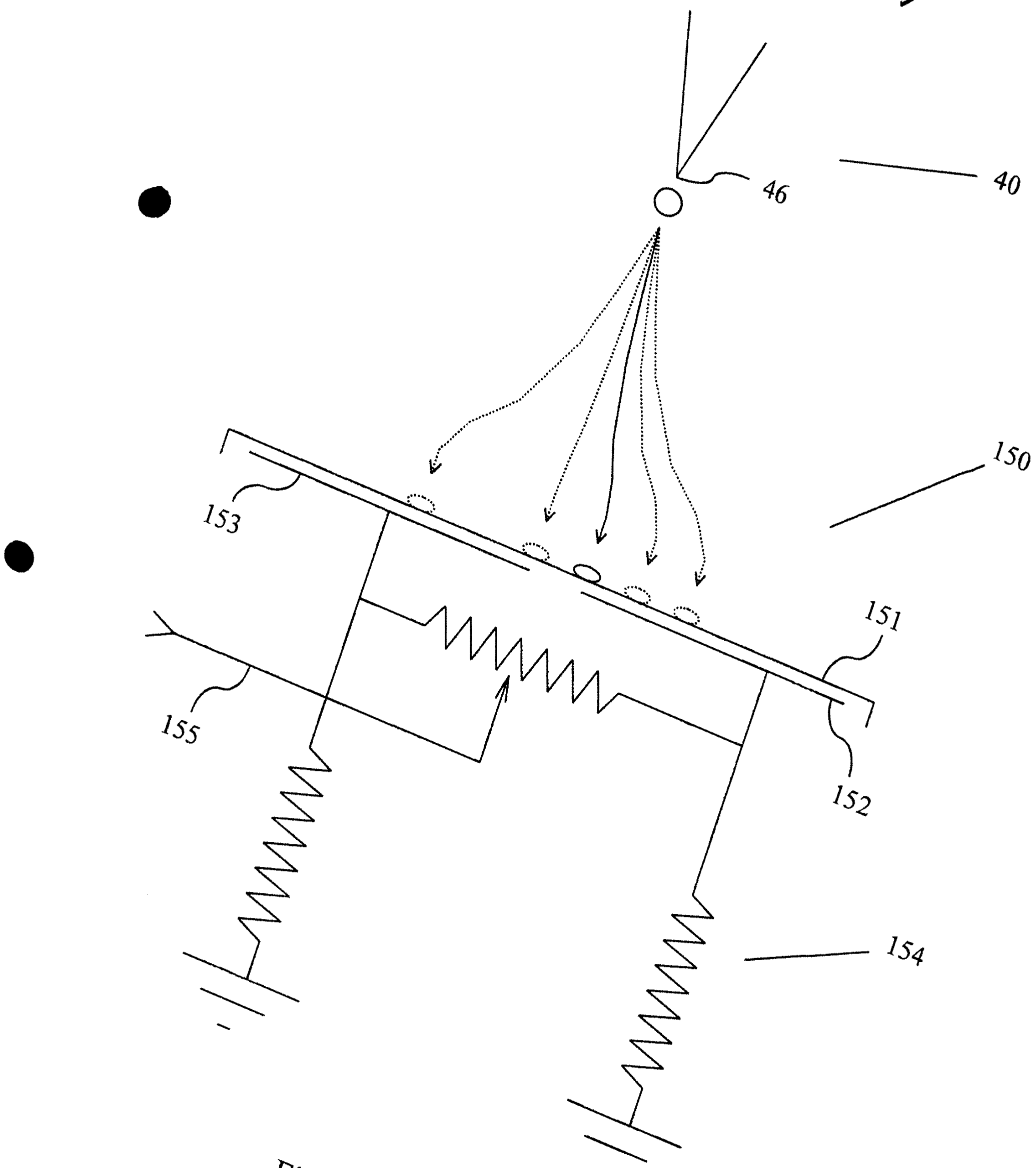

Fig. 29

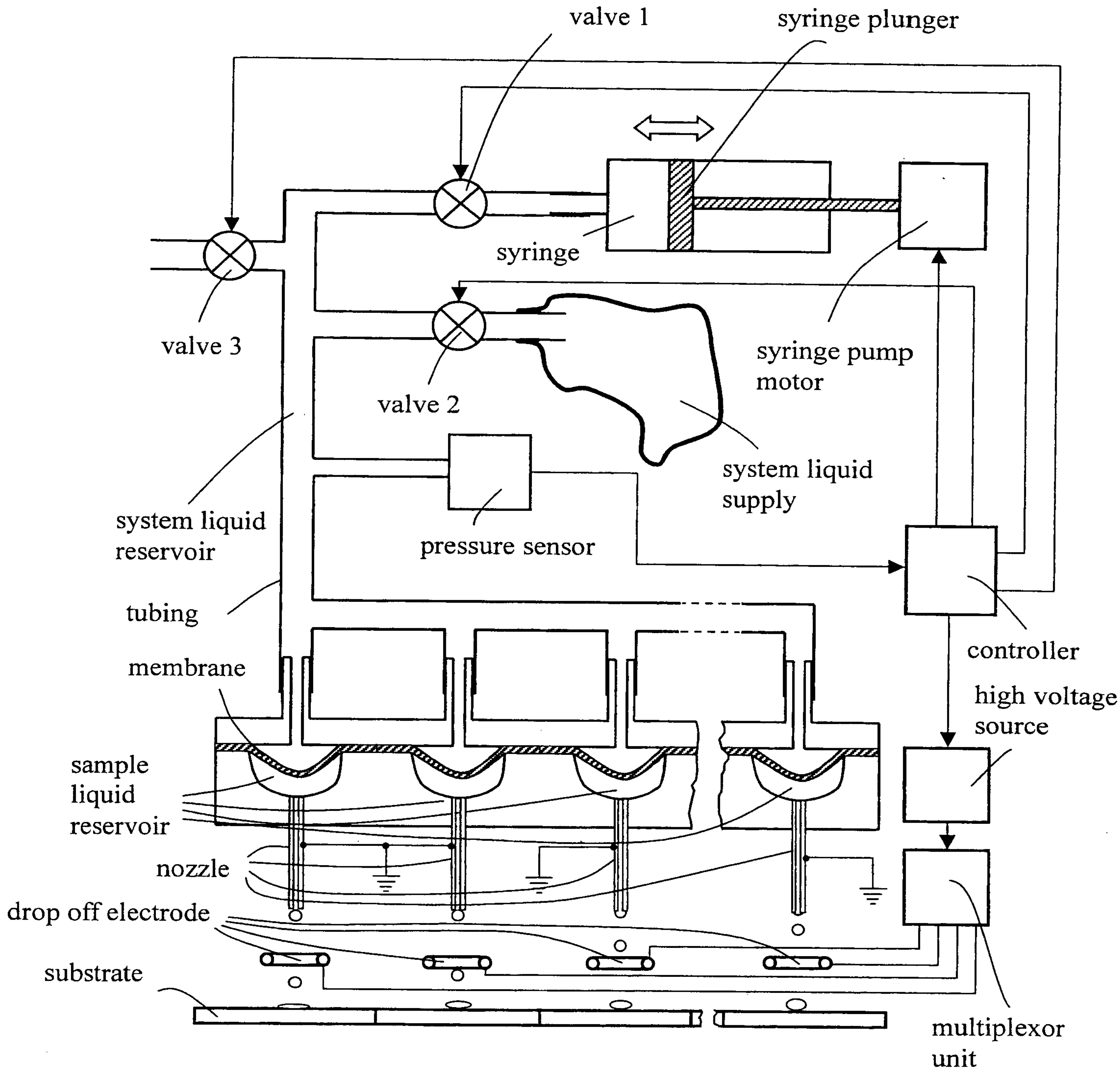

Fig. 30, A multichannel dispensing assembly.

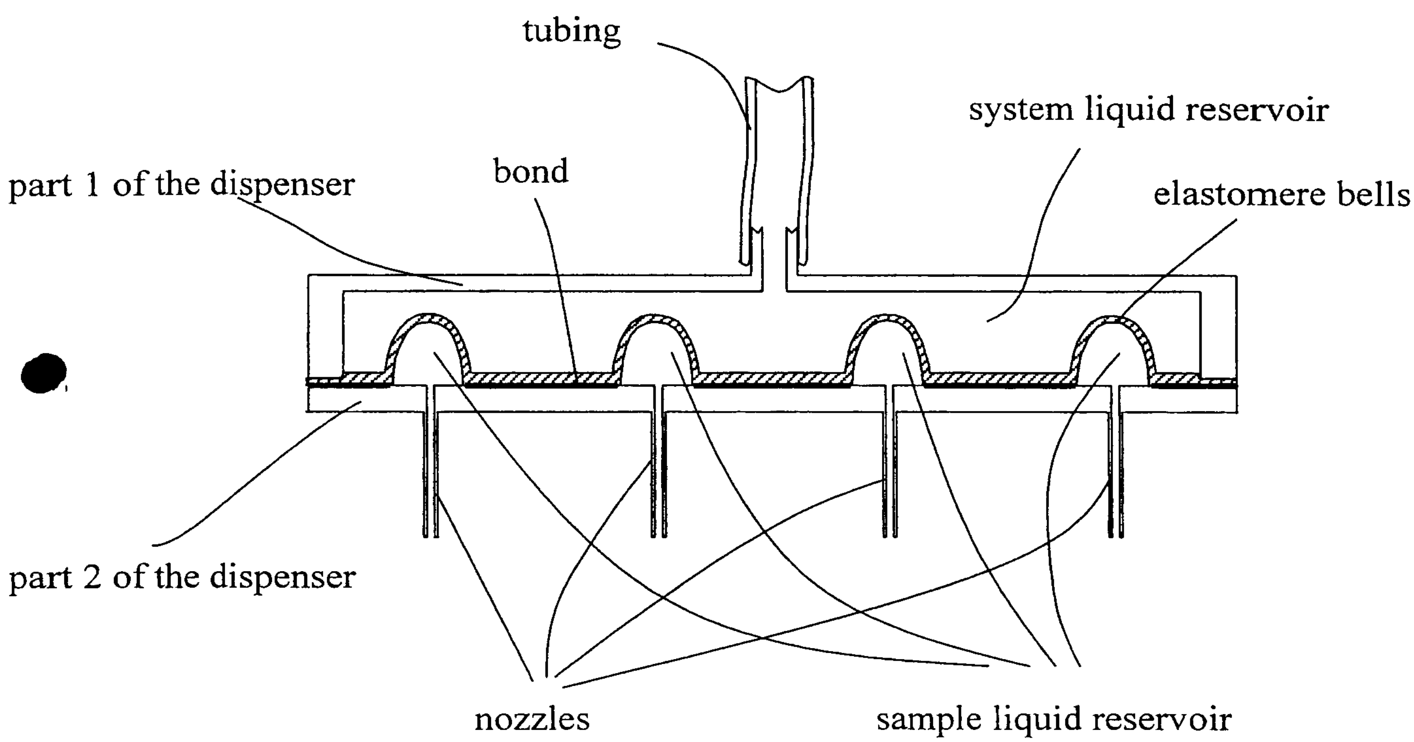

FIG 31

Block of four dispensers with flexible bells.

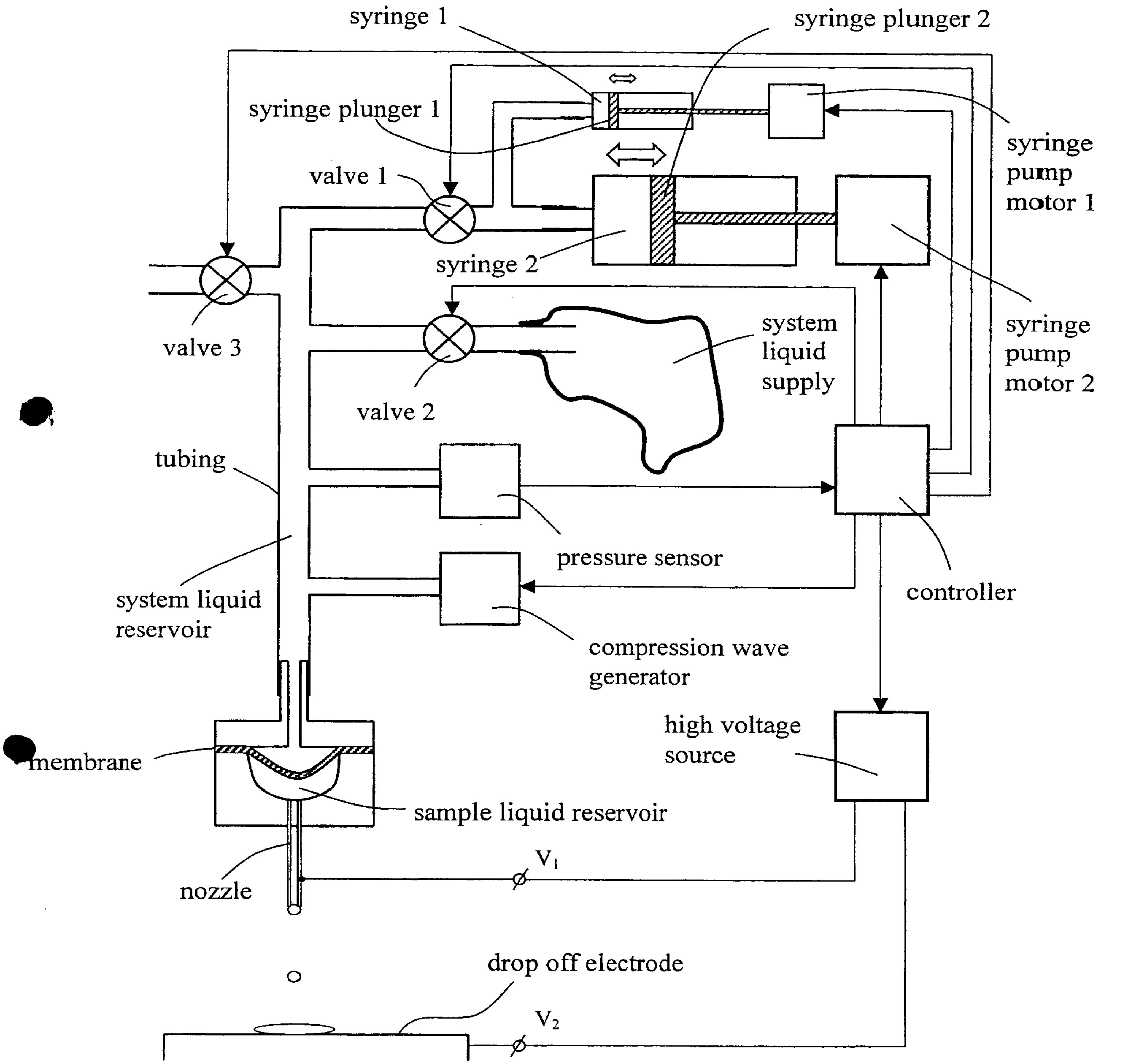

Fig. 32, [illegible] Dispensing assembly using two syringes: one for precision dispensing and the other one for large dynamic range

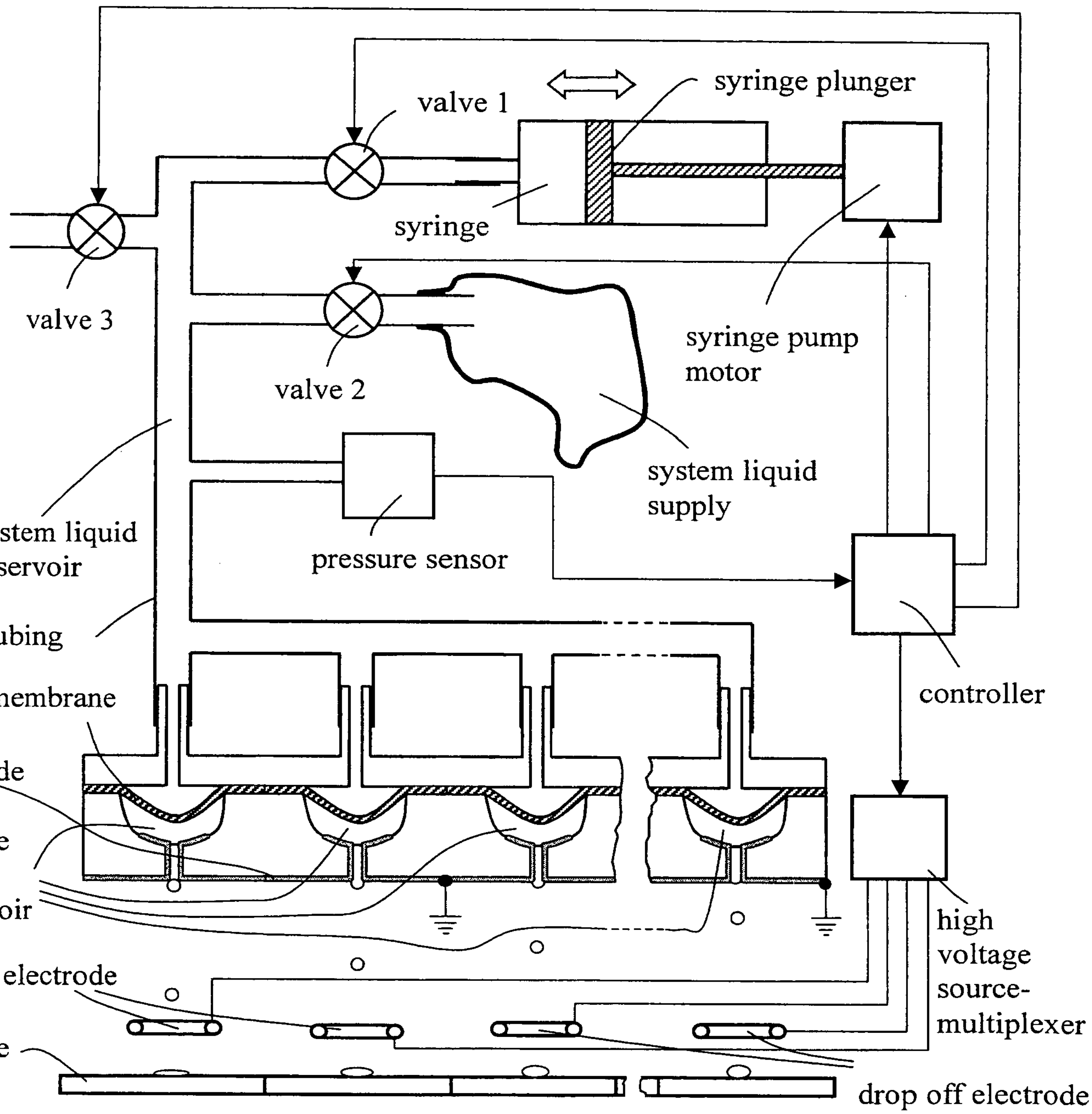

Fig. 33. Dispensing assembly without nozzles